THE REACTIONS AND ISOMERISM OF β-AMINOCROTONONITRILE

and

THE REACTION OF AROMATIC GRIGNARD REAGENTS WITH β-AMINOCROTONONITRILE

A Thesis

by

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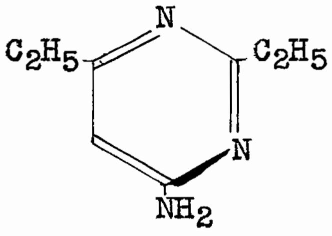
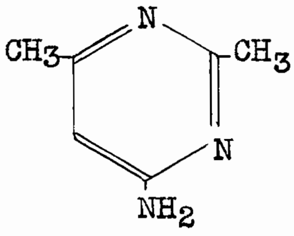
HISTORICAL

As early as 1848, Frankland and Kolbe (26) observed the reaction of propionitrile with metallic sodium in the absence of a solvent. The reaction products were sodium cyanide, ethane, and an organic base which they named cyanoethene (I). The structure of (I) was elucidated by Ernst von Meyer (41) in 1889, and was shown to be a derivative of aminopyrimidine. In 1869, A.G. Bayer (6,7) investigated the behavior of acetonitrile toward metallic sodium under similar conditions. The main product was an organic base, cyanomethene (II), which was related to cyanoethene. E. von Meyer (39,40) investigated the reaction of propionitrile with metallic sodium in benzene solution. Instead of the expected cyanoethene, he obtained a dimer of propionitrile, which he named 'dipropionitrile'. It was α-methyl-β-aminovaleronitrile (III). His co-worker, R. Holtzwart (31,32), treated acetonitrile with metallic sodium in ether and benzene solutions and observed the formation of a dimer of acetonitrile, which he named 'diacetonitrile'. It was β-aminocrotononitrile (XII). Holtzwart (32) reacted sodium with a mixture of benzo-



(I)



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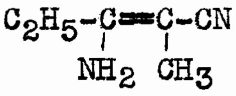
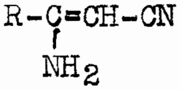


$C_2H_5-\underset{NH_2}{C}=\underset{CH_3}{C}-CN$

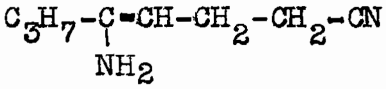
(III)

nitrile and acetonitrile in benzene, and obtained β-phenyl-β-aminoacrylonitrile. E. von Meyer (41, 42, 47) also investigated the behavior of metallic sodium toward mixtures of aromatic nitriles and acetonitrile, and obtained similar dimers of the general formula (IV).


$$R-\underset{NH_2}{\underset{|}{C}}=CH-CN$$

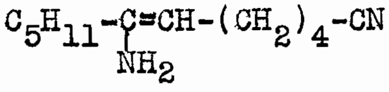
(IV)

Dimers were obtained having R= p-ethoxyphenyl, p-tolyl, 2-chloro phenyl, 3-chlorophenyl, 4-chlorophenyl. Sonn (57) prepared β-imino-β-(4-methoxyphenyl)propionitrile in 1918 by the reaction of sodium with a mixture of p-methoxybenzonitrile and acetonitrile. Von Meyer (41) treated a mixture of benzonitrile and propionitrile with metallic sodium, and obtained β-amino-β-phenyl-α-methyl-acrylonitrile. R. Wache (63) found that the condensation of butyronitrile by sodium produced a quite different type of dimer. The γ-hydrogen, instead of the α-hydrogen, of the second molecule of nitrile took part in the condensation to produce (V).


$$C_3H_7-\underset{NH_2}{\underset{|}{C}}=CH-CH_2-CH_2-CN$$

(V)

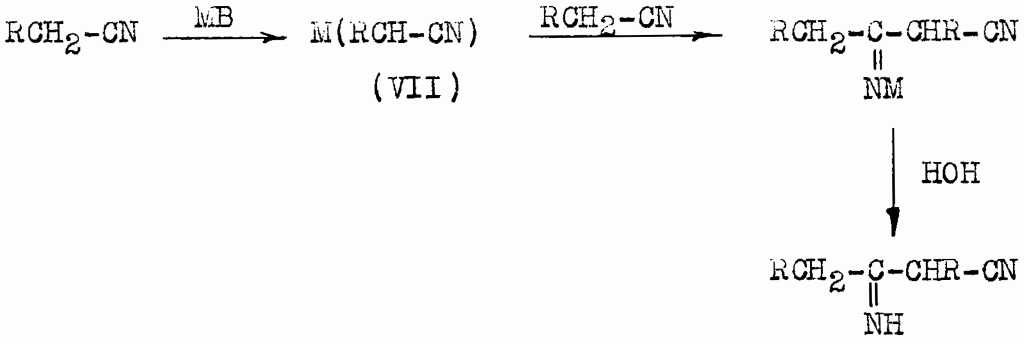
The same type of condensation occurred with sodium and capronitrile to produce (VI).


$$C_5H_{11}-\underset{NH_2}{\underset{|}{C}}=CH-(CH_2)_4-CN$$

(VI)

Dornow, Kuhlke, and Baxmann (20), in 1949, found that β-amino-β-phenylacrylonitrile, and its 4-substituted derivatives were several hundred times sweeter than cane sugar. However, their toxicity prevented their use as artificial sweetening agents.

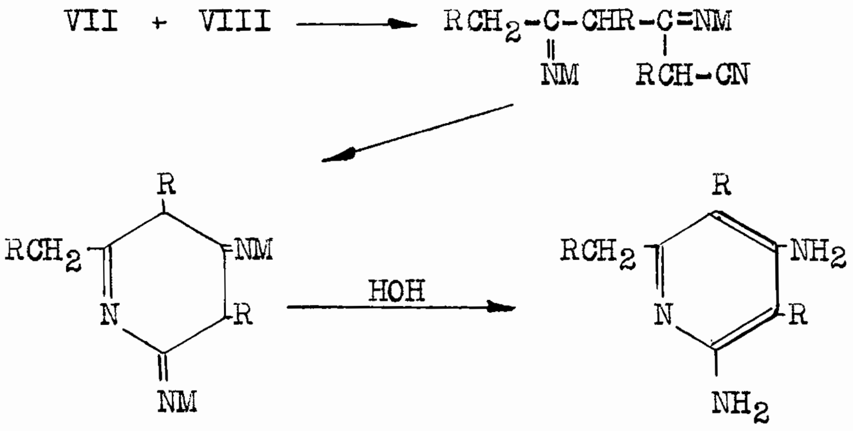
The reaction of sodium with nitriles having α-hydrogen atoms was by no means confined to acetonitrile and propionitrile. Other nitriles, such as valeronitrile and phenylacetonitrile, condensed with sodium to form similar dimers (51). Reynolds, Humphlett, Swamer, and Hauser (51) found that other metallic basic reagents (MB) were just as effective as sodium in many of the condensations. Sodium hydride, sodium azide, and diisopropylaminomagnesium bromide were all used as condensing agents in the place of metallic sodium. The general reaction was given by the following equation:



$$RCH_2\text{-}CN \xrightarrow{MB} \underset{(VII)}{M(RCH\text{-}CN)} \xrightarrow{RCH_2\text{-}CN} RCH_2\text{-}\underset{\underset{NM}{\|}}{C}\text{-}CHR\text{-}CN \qquad (VIII)$$

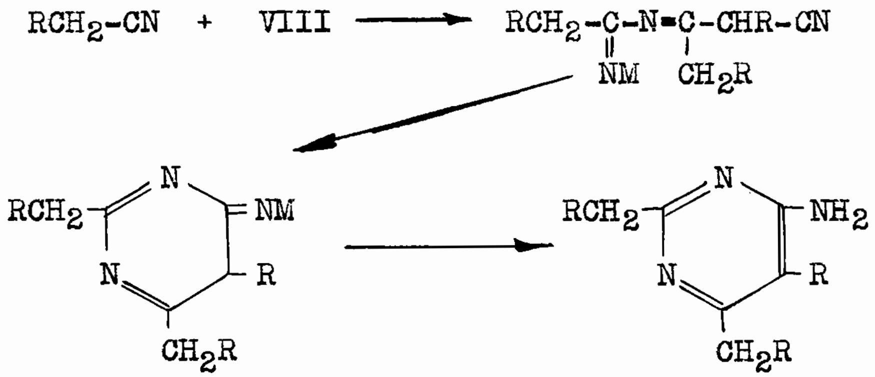
$$\xrightarrow{HOH} RCH_2\text{-}\underset{\underset{NH}{\|}}{C}\text{-}CHR\text{-}CN$$

Under other conditions, cyclic trimers of pyridine or pyrimidine types (IX and X respectively) were produced by the following reactions:



$$VII + VIII \longrightarrow RCH_2\text{-}\underset{\underset{NM}{\|}}{C}\text{-}CHR\text{-}\underset{\underset{RCH\text{-}CN}{|}}{C}{=}NM$$

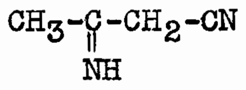
(IX)



It was found that a basic reagent produced mainly the dimer in refluxing ethyl ether, while the same reagent in refluxing n-butyl ether produced mainly the trimer. The pyrimidine trimer with R = H was formed in 50% yield by refluxing acetonitrile with sodium in n-butyl ether. Such a trimer had been reported in good yield by Keller (36) in 1885, and by Schwarze (55) in 1890.

Claisen (19) reported the preparation of β-aminocrotononitrile in small yield by heating 5-methylisoxazol with a solution of ammonia in absolute methanol in a tube at 100°.

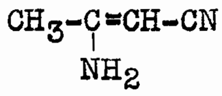
Diacetonitrile was shown to be an aminonitrile, and not a dinitrile as the name implied. Two tautomeric structures were proposed for diacetonitrile by von Meyer (42). The structures were the following:



$CH_3-\underset{\underset{NH}{\|}}{C}-CH_2-CN$

Ketimine (XI)

β-Iminobutyronitrile



$CH_3-\underset{\underset{NH_2}{|}}{C}=CH-CN$

Enamine (XII)

β-Aminocrotononitrile

The reaction of acetonitrile with sodium required three molecules of acetonitrile for two atoms of sodium. The first step of the mechanism of reaction, as proposed by Holtzwart (32), was the decomposition of a molecule of acetonitrile by a sodium atom, which then combined with the cyano group to form sodium cyanide, and liberating a methyl group. A second atom of sodium simultaneously substituted for a hydrogen atom of the second molecule of acetonitrile to form sodium acetonitrile and a hydrogen atom, which combined with the methyl group to form methane. The sodium acetonitrile immediately reacted with the third molecule of acetonitrile, forming the sodium salt of β-aminocrotononitrile. The sodium salt of β-aminocrotononitrile was never isolated by itself, but always occurred with a molecule of sodium cyanide. The reaction mechanism was expressed by the following equations:

$$\begin{array}{c} Na \\ Na \end{array} + \begin{array}{c} CH_3\text{-}CN \\ CH_3\text{-}CN \end{array} \longrightarrow \begin{array}{c} NaCN + CH_3{\cdot}H \\ + CH_2Na\text{-}CN \end{array} \qquad 1)$$

$$CH_2Na\text{-}CN + CH_3\text{-}CN \longrightarrow C_4H_5NaN_2 \qquad 2)$$

$$C_4H_5NaN_2 + HOH \longrightarrow C_4H_6N_2 + NaOH \qquad 3)$$

Equation 3) represented the decomposition of the sodium salt of β-aminocrotononitrile by water, to yield free β-aminocrotononitrile.

To establish the existence of the sodium acetonitrile molecule, Holtzwart reacted sodium metal with an equimolecular mixture of acetonitrile and ethyl iodide. He obtained a mixture of sodium cyanide and sodium iodide, and a small amount of a liquid, which he claimed was butyronitrile formed in the reaction:

$$CH_3\text{-}CH_2\text{-}I + NaCH_2\text{-}CN \longrightarrow NaI + CH_3\text{-}CH_2\text{-}CH_2\text{-}CN$$

His proof was, however, not very conclusive.

REACTIONS OF β-AMINOCROTONONITRILE

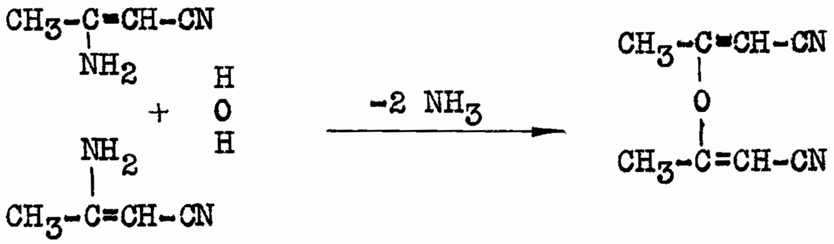
β-Aminocrotononitrile was found to be a very versatile compound, reacting in many ways with various reagents. The two main types of reactions of β-aminocrotononitrile were 1) cyclization to substituted pyridine or dihydropyridine compounds, and 2) substitution of the α-hydrogen, or the hydrogen of the β-amino group, to yield branched chain compounds.

Holtzwart (32) noted that a reaction took place when β-aminocrotononitrile was heated with water. The main product was a water-insoluble compound, melting at 293°, and having a formula, $C_8H_8N_2O$. The by-products were ammonia, hydrogen cyanide, α-cyanoacetone, and α-hydroxyacetone. The α-hydroxyacetone was likely formed by the further decomposition of the cyanoacetone.

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-CN \;+\; HOH \longrightarrow CH_3-\underset{\underset{O}{\|}}{C}-CH_2-OH \;+\; HCN$$

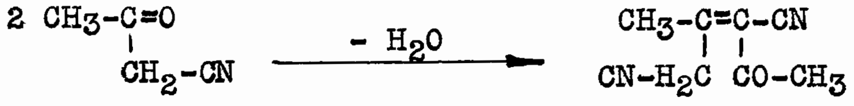
This would account for the presence of the hydrogen cyanide.

The $C_8H_8N_2O$ was believed to be formed by the reaction of two molecules of β-aminocrotononitrile with one molecule of water, eliminating two molecules of ammonia, to yield (XIII).



(XIII)

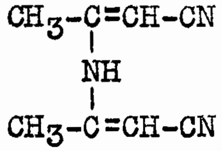
Von Meyer (42) considered the reaction to be the splitting out of water from two molecules of cyanoacetone to form (XIV). The reaction was represented by the following equation:



$$2\ CH_3-\underset{\underset{\displaystyle CH_2-CN}{|}}{C}=O \xrightarrow{-\ H_2O} CH_3-\underset{\underset{\displaystyle CN-H_2C}{|}}{C}=\underset{\underset{\displaystyle CO-CH_3}{|}}{C}-CN \qquad (XIV)$$

Neither of these structures (XIII and XIV) stood up under the light of chemical evidence. In 1902, Moir (49) showed that the compound $C_8H_8N_2O$ was very stable. It was unaffected by boiling with 10% alcoholic or aqueous sodium hydroxide solutions, boiling with acetic anhydride, heating with 70% sulphuric acid at 120°, heating at 80° with fuming sulphuric acid, and was unaffected by acetyl chloride, hydroxylamine, or nitrous acid. It was only slightly affected by boiling dilute nitric acid, or by permanganate. It immediately reduced chromic acid in acetic acid solution, but no isolatable products were formed. One of the nitrogen atoms was basic in character. When dissolved in alkali, metallic derivatives were formed, and found to be phenolic in character, because the addition of carbon dioxide or ammonium salts to their solutions caused the precipitation of the original material. Zinc dust distillation produced a small amount of liquid with a distinct pyridine-like odor. When $C_8H_8N_2O$ was heated with concentrated hydrobromic acid in a sealed tube for six hours at 170°, a large quantity of 2,4-dimethyl-6-hydroxypyridine was isolated, presumably formed by the replacement of the cyano group by a hydrogen atom. Ammonia and carbon dioxide were found as by-products. This evidence fixed the structure of $C_8H_8N_2O$ as 2,4-dimethyl-3-cyano-6-hydroxypyridine. As further proof, the $C_8H_8N_2O$ was chlorinated with phosphorus pentachloride to the 6-chloropyridine compound, which yielded 3-cyano-2,4-dimethyl pyridine, when hydrogenated.

Holtzwart (32) investigated the reaction of β-aminocrotononitrile with acetyl chloride in absolute ether, and isolated a white crystalline compound, melting at 223°, and having the formula $C_8H_9N_3$. He assumed the structure of it to be (XV).



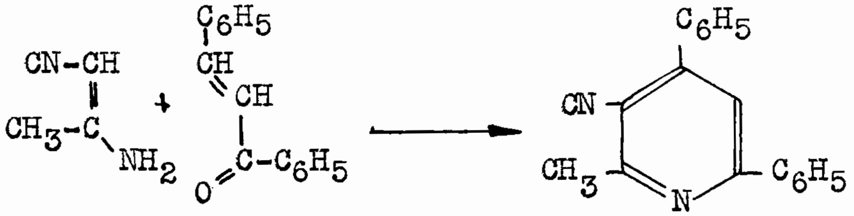
$$\begin{array}{l} CH_3-C=CH-CN \\ \qquad | \\ \quad\; NH \\ \qquad | \\ CH_3-C=CH-CN \end{array}$$

(XV)

The same product was produced by the action of benzoyl chloride on β-aminocrotononitrile. The reaction of β-aminocrotononitrile with benzyl cyanide, cyanoacetic acid, anthranilic acid, ethylene dibromide, ethyl chlorocarbonate, or alcoholic hydrogen chloride all produced the same compound. The best method of preparation was by the action of anhydrous zinc chloride and ammonia. The compound formed a bright yellow double salt with platinic chloride, and formed a monoacetyl derivative with acetic anhydride. The action of nitrous acid liberated nitrogen and precipitated the compound previously identified as 2,4-dimethyl-3-cyano-6-hydroxy pyridine. This established the structure of $C_8H_9N_3$ as 3-cyano-6-amino-2,4-lutidine.

β-Aminocrotononitrile reacted very readily with other compounds, which contained carbonyl groups, to form substituted pyridines and dihydropyridines. The reaction with unsaturated ketones produced monocyanopyridines. Benzalacetophenone in alcohol (45) in the presence of sodium ethoxide combined with β-aminocrotononitrile to yield 3-cyano-2-methyl-4,6-diphenyl pyridine (XVI), needles melting at 116°C.

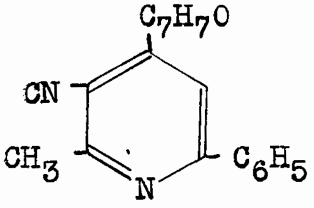
pyridine, as indicated in the reaction:



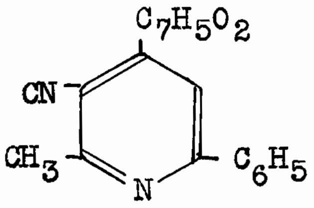
(XVI)

The 3-cyanopyridine compound (XVI) was hydrolysed by heating at 260° with hydrochloric acid to the corresponding 3-carboxylic acid derivative, which in turn was oxidized by potassium permanganate to 4,6-diphenylquinolinic acid.

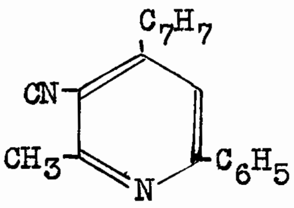
Similar condensations were carried out by Meyer (45) with anisalacetophenone and piperonalacetophenone to prepare the corresponding cyanopyridines (XVII and XVIII). 1-Phenyl-3-(p-tolyl)propane reacted with β-aminocrotononitrile to yield 3-cyano-2-methyl-6-phenyl-4-(p-tolyl)pyridine (XIX).



(XVII)



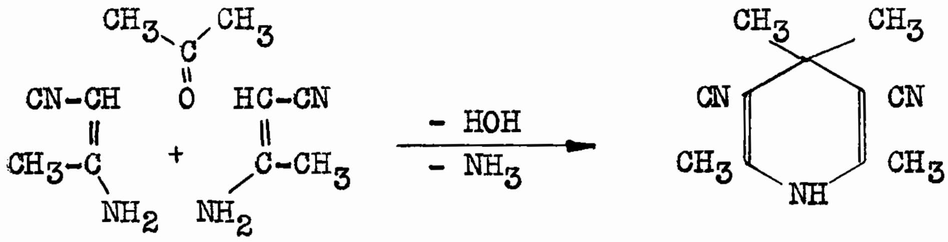
(XVIII)



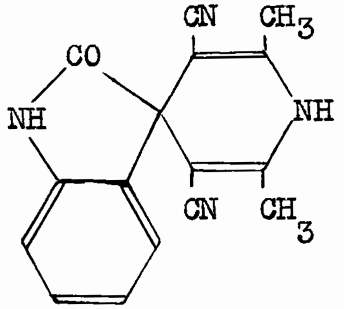
(XIX)

Von Meyer (47) investigated the reaction between saturated ketones and β-aminocrotononitrile, isolating 3,5-dicyano-1,4-dihydropyridines in yields from 34% to 80%. Two molecules of β-aminocrotononitrile reacted with one molecule of the ketone in the presence of one molecule of hydrochloric acid in alcohol at 5°. Oxidation of the dihydropyridine compounds was readily accomplished with chromic acid in acetic acid solution.

The reaction with acetone was considered to be the following:



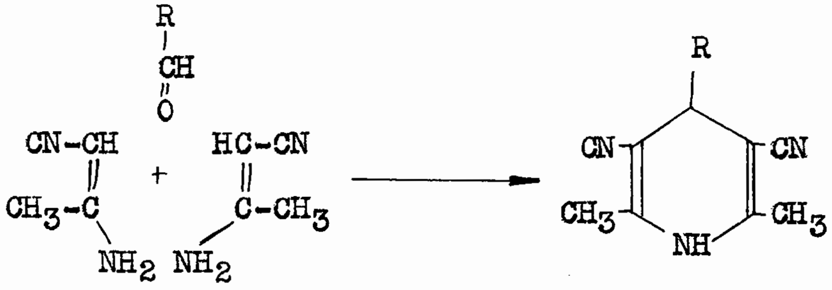
Investigations were carried out by von Meyer (47) using methyl ethyl ketone, methyl propyl ketone, methyl benzyl ketone, diethyl ketone, cyclohexanone, and methyl cyclohexanone. The reaction with diethyl ketone gave the poorest yield (34%), and the reaction with cyclohexanone gave the highest yield (80%). It was found to be impossible to hydrolyse the cyano groups to the corresponding carboxylic acids. When the dihydropyridines prepared from ketones containing the CH_3CO- grouping were oxidized with chromic acid in glacial acetic acid solution, the hydrogen atom of the NH group and the R- group on the 4- position were lost, leaving the substituted 4-methylpyridine compounds. The yields in the oxidation reactions were very high. Walther (65) found that isatin reacted with β-aminocrotononitrile in the manner of a ketone to produce the dihydropyridine compound (XX).



(XX)

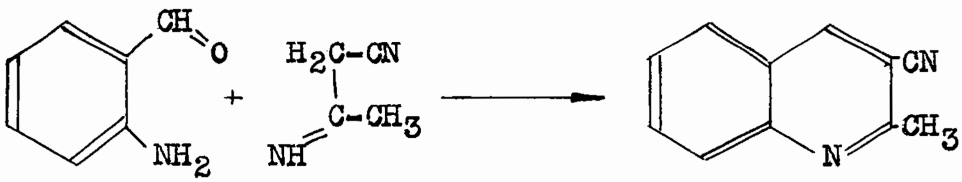
It was shown by von Meyer (45) that aldehydes reacted with β-aminocrotononitrile in a manner similar to ketones.

Formaldehyde, acetaldehyde, and benzaldehyde reacted in glacial acetic acid solution with β-aminocrotononitrile to yield 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridine, and the 4-methyl-, and 4-phenyl- derivatives, as in the equation:



$R = H,\ CH_3\ ,\ C_6H_5\ .$

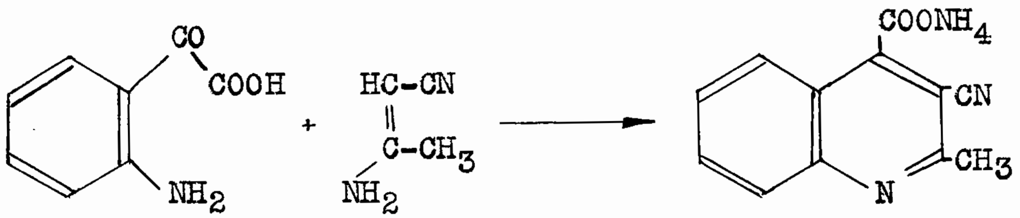
Substituted benzaldehydes reacted to give dihydropyridine compounds with the correspondingly substituted phenyl group in the 4-position. An exception to this behavior was found by von Meyer. The reaction between β-aminocrotononitrile and o-aminobenzaldehyde did not produce the expected 4-(o-aminophenyl)pyridine compound, but 2-methyl-3-cyanoquinoline was formed according to the reaction:



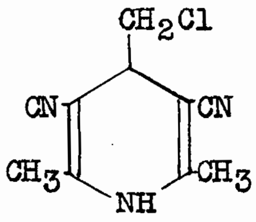
In 1897, Mohr (48) investigated the reaction between β-aminocrotononitrile and salicylaldehyde, expecting to obtain a 3-cyanoquinoline derivative. Instead, he found that two molecules of salicylaldehyde combined with one molecule of β-aminocrotononitrile to eliminate two molecules of water, yielding a crystalline compound, $C_{18}H_{14}N_2O_2$, whose constitution has not yet been determined. In general, the

1,4-dihydropyridines were very readily dehydrogenated by treatment in alcohol with nitrous acid.

Walther (65) and von Meyer (46) found that isatic acid reacted with β-aminocrotononitrile to yield the ammonium salt of 2-methyl-3-cyanoquinoline-4-carboxylic acid, according to the reaction:



In 1922, Benary and Lowenthal (11) investigated the condensation of β-aminocrotononitrile with β,β'-dichlorodiethyl ether, $(ClC_2H_4)_2O$, and isolated 4'-chloro-3,5-dicyano-1,4-dihydrocollidine (XXI). When this was treated in methanol with

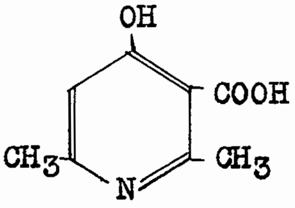


(XXI)

potassium cyanide, two products were isolated. They were 4'-cyano-3,5-dicyano-1,4-dihydrocollidine, and 4'-carbimino-3,5-dicyano-1,4-dihydrocollidine. The treatment of the 4'-cyano pyridine in glacial acetic acid solution with sodium nitrite yielded 4',3,5-tricyanocollidine. Treatment of the 4'-chloro pyridine in glacial acetic acid with sodium nitrite yielded the oxime of 4'-aldehydo-3,5-dicyano-1,4-dihydrocollidine.

Dubsky (21) reacted β-aminocrotononitrile with alkaline hydrogen peroxide. He isolated a small amount of 2,4,6-trimethyl

-3,5-dicyano-1,4-dihydropyridine. The hydrogen peroxide had oxidized a small portion of the alcoholic solvent to acetaldehyde, which had then reacted with the β-aminocrotononitrile. Von Meyer (43,45) isolated 4-hydroxy-2,6-dimethylpyridine-3-carboxylic acid (XXII) from the reaction between β-aminocrotononitrile and ethyl acetoacetate in the presence of a small quantity of pyridine.



(XXII)

Von Meyer (46) found that the reaction of succinic acid and other α-hydroxy acids with β-aminocrotononitrile yielded 2,4-dimethyl-3-cyano-6-hydroxypyridine

In addition to the cyclization reactions, β-aminocrotononitrile underwent numerous reactions which involved the active hydrogen atoms on both the α-carbon atom and the β-amino group.

Chlorination, bromination, and iodination of β-aminocrotononitrile were accomplished by von Meyer (42,43,47). The treatment of an aqueous solution of β-aminocrotononitrile with an excess of bleaching powder yielded β-chloroaminocrotononitrile as white needles, melting at 120°. Bromination was accomplished using bromine in caustic potash, and also by cyanogen bromide in benzene. β-Bromoaminocrotononitrile was crystallized as long white needles, melting at 123°. β-Iodoaminocrotononitrile, melting at 85°, was precipitated when β-aminocrotononitrile was treated with iodine in potassium iodide solution at room temperature.

When heated with hydrochloric acid, β-iodoaminocrotononitrile decomposed into ammonia, iodine monochloride, and cyanoacetone.

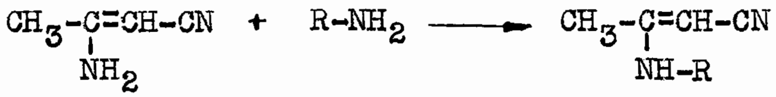
Von Meyer (45) found that aromatic amines and diamines reacted very readily with β-aminocrotononitrile in glacial acetic acid solution. The product, listed in Table I, were all crystalline, and easily resolved by hydrochloric acid into β-aminocrotononitrile and the respective amine.

TABLE I

N-SUBSTITUTED β-AMINOCROTONONITRILES.

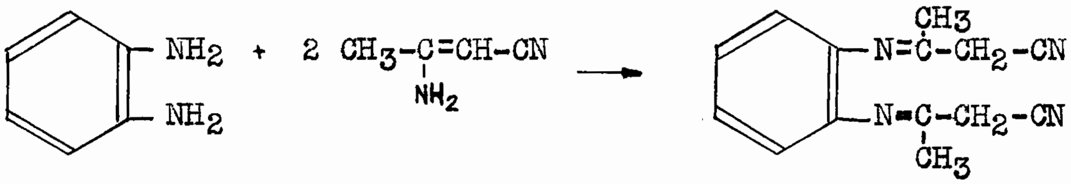
Amine - R	Crystalline Form	Melting Point
Phenyl	White needles	115°
o-Tolyl	Pearly leaflets	73°
p-Tolyl	White needles	102°
m-Tolyl	White prisms	79°
Benzyl	White needles	79°
α-Naphthyl	Gleaming leaflets	112°
β-Naphthyl	Brown leaflets	172°
m-Chlorophenyl	White needles	136°
p-Chlorophenyl	White leaflets	114°
p-Hydroxyphenyl	Brown needles	120°
p-Ethoxyphenyl	White needles	138°
p-Carboxyphenyl	White needles	206°
m-Carboxyphenyl	Needles	158°

The reaction with amines was assumed to be the following:



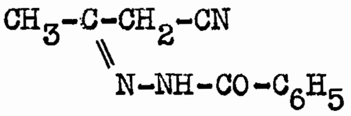
$$CH_3-\underset{NH_2}{\underset{|}{C}}=CH-CN + R-NH_2 \longrightarrow CH_3-\underset{NH-R}{\underset{|}{C}}=CH-CN$$

With diamines, two molecules of β-aminocrotononitrile reacted with one molecule of the diamine, as in the following reaction:



In this manner, the three diaminobenzenes were reacted with β-aminocrotononitrile to form the crystalline substituted products.

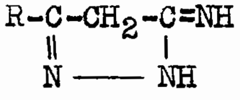
The reaction with semicarbazide, or its hydrochloride, thiosemicarbazide, benzoyl hydrazine, or with hydrazine itself was not as simple as the reaction with aromatic amines. Von Meyer (45) investigated the reaction of β-aminocrotononitrile with semicarbazide, and its hydrochloride, and isolated two isomeric semicarbazones. The stable derivative melted at 134°, and the labile derivative melted first at 165°, then solidified, melting again at 220°. Two similar modifications were isolated when thiosemicarbazide was used. The stable thiosemicarbazone melted at 106°. The labile derivative melted first at 132°, then solidified, melting again at 165°. When β-aminocrotononitrile was reacted with benzoyl hydrazine, only one product was isolated, the benzoylhydrazone of α-cyanoacetone (XXIII).



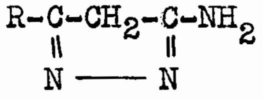
$$CH_3\text{-}C(=N\text{-}NH\text{-}CO\text{-}C_6H_5)\text{-}CH_2\text{-}CN$$

(XXIII)

In 1915, von Meyer (47) investigated the reactions of various β-aminonitriles with hydrazine without ever isolating the expected hydrazones. The hydrazones had cyclized to iminopyrazolones (XXIV), or to the isomeric aminopyrazole (XXV).

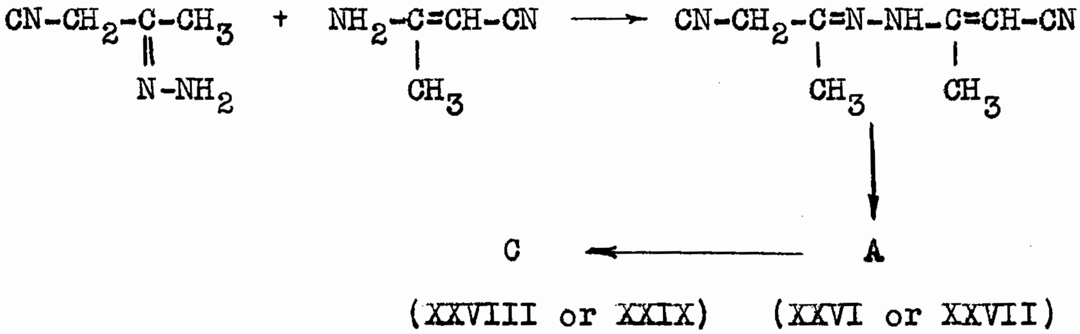


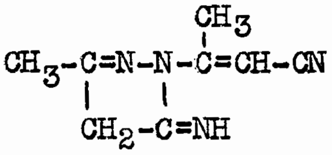
(XXIV)

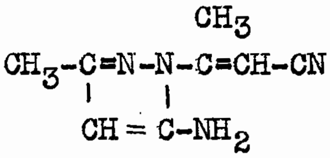


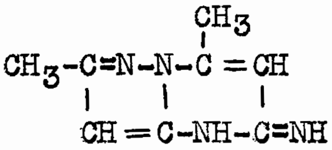
(XXV)

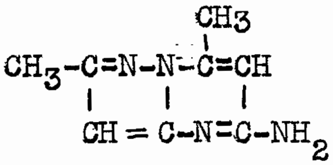
When the reaction of hydrazine with β-aminocrotononitrile was studied, the corresponding pyrazolone was not found. Instead, two isomeric compounds with the formula $C_8H_{10}N_4$ were isolated. The course of reaction was considered to be the following:




(XXVI)

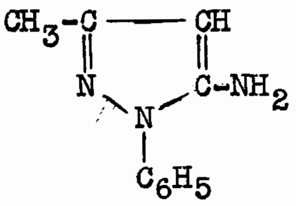

(XXVII)


(XXVIII)


(XXIX)

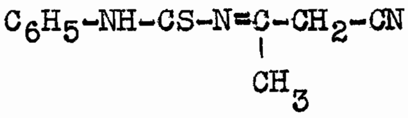
However, no definite evidence was advanced to determine the correct structures. Compound A could be diazotized, thus favoring the free amino grouping of (XXVII). On the other hand, treatment of compound A with nitrous acid in the absence of hydrochloric acid produced a red precipitate, insoluble in sodium hydroxide solution. This was presumably an isonitroso derivative, thus favoring the $-CH_2-$ grouping of (XXVI). Compound C could be diazotized and coupled, and also formed no isonitroso derivative, favoring the structure (XXIX).

Brust (17) and Walther (64) found that the reaction of β-aminocrotononitrile with phenylhydrazine yielded 1-phenyl-3-methyl-5-aminopyrazole (XXX).



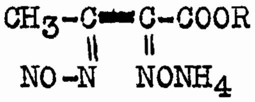
(XXX)

The reaction of β-aminocrotononitrile with phenyl isothiocyanate at 140-150° yielded the following compound: (33).



$$C_6H_5-NH-CS-N=\underset{\underset{CH_3}{|}}{C}-CH_2-CN$$

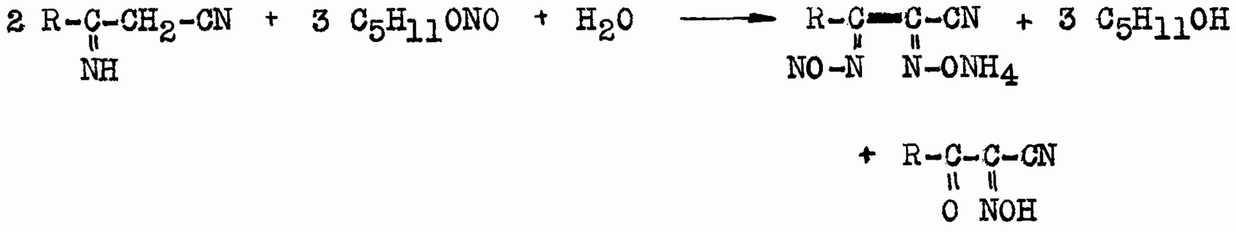
Euler (22) investigated the action of nitrous acid on β-aminocrotonic ester and obtained a nitrosimine (XXXI).



$$CH_3-\underset{\underset{NO-N}{\parallel}}{C}=\underset{\underset{NONH_4}{\parallel}}{C}-COOR$$

(XXXI)

Lublin (37) investigated the action of amyl nitrite on dinitriles having an imino grouping similar to β-aminocrotonic ester. It was found that only compounds containing the $-\underset{\parallel}{C}-CH_2-$ group yielded the nitrosimine reaction with amyl nitrite, according to the reaction:

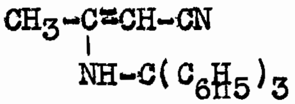


$$2\,R-\underset{\underset{NH}{\parallel}}{C}-CH_2-CN + 3\,C_5H_{11}ONO + H_2O \longrightarrow R-\underset{\underset{NO-N}{\parallel}}{C}=\underset{\underset{N-ONH_4}{\parallel}}{C}-CN + 3\,C_5H_{11}OH$$

$$+\ R-\underset{\underset{O}{\parallel}}{C}-\underset{\underset{NOH}{\parallel}}{C}-CN$$

The oxime was not obtained when R was methyl, but was obtained when R was phenyl or p-tolyl.

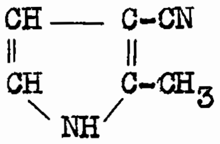
Benary and Lorth (9) treated β-aminocrotononitrile with triphenylmethyl chloride in the presence of pyridine, and obtained β-triphenylmethylaminocrotononitrile (XXXII).



$$\begin{array}{l} CH_3-\underset{\displaystyle NH-C(C_6H_5)_3}{\underset{|}{C}}=CH-CN \end{array}$$

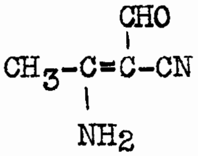
(XXXII)

Strain (60), and Benary and Lowenthal (11) reacted α,β-dichlorodiethyl ether, $CH_2Cl-CHCl-O-C_2H_5$, in 10% aqueous ammonia with β-aminocrotononitrile, and isolated 2-methyl-3-cyanopyrrole (XXXIII).

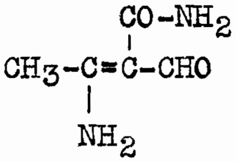


(XXXIII)

Benary and Schmidt (12) found that the condensation of β-aminocrotononitrile with acid chlorides in pyridine gave results comparable to those obtained by the condensation of β-aminocrotonic esters under similar conditions. With the β-aminocrotonic esters and the acid chlorides, both the C- and N- derivatives were obtained, depending on the nature of the chloride. The reaction of the sodium salt of β-aminocrotonic ester with esters gave only N- derivatives. This work on esters was extended to β-aminocrotononitrile to determine the effect of the cyano group upon the introduction of acid residues. The reaction of β-aminocrotononitrile with esters yielded both the N- and C- derivatives, depending on the conditions of the reaction. Von Meyer (46) investigated the reaction between β-aminocrotononitrile and ethyl formate and potassium ethylate in ether solution, and isolated α-formyl-β-aminocrotononitrile (XXXIV). Treatment of the potassium salt of (XXXIV) with hydrogen chloride in benzene suspension produced the carbamino derivative (XXXV).

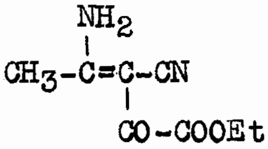

$CH_3-C(NH_2)=C(CHO)-CN$

(XXXIV)

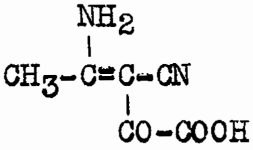

$CH_3-C(NH_2)=C(CO-NH_2)-CHO$

(XXXV)

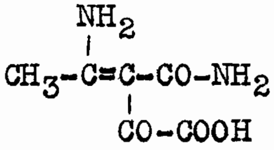
Von Meyer (46) also investigated the reaction between ethyl oxalate and β-aminocrotononitrile, isolating the α-ethoxalyl-β-aminocrotononitrile (XXXVI), which was readily hydrolysed to the corresponding acid (XXXVII), and carbamino derivative (XXXVIII).


$CH_3-C(NH_2)=C(CO-COOEt)-CN$

(XXXVI)

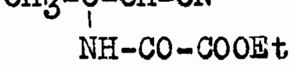

$CH_3-C(NH_2)=C(CO-COOH)-CN$

(XXXVII)

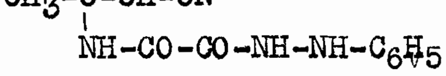

$CH_3-C(NH_2)=C(CO-COOH)-CO-NH_2$

(XXXVIII)

Benary and Schmidt (12) condensed β-aminocrotononitrile with diethyl oxalate in the presence of sodium ethylate, and isolated the N- derivative (XXXIX). (XXXIX) yielded a phenylhydrazone which was decomposed by acid into $C_6H_5-NH-NH-CO-CO-NH_2$. Such a


$CH_3-C(NH-CO-COOEt)=CH-CN$

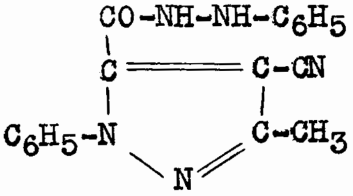
(XXXIX)


$CH_3-C(NH-CO-CO-NH-NH-C_6H_5)=CH-CN$

(XL)

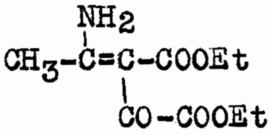
decomposition product could only come from the N- substituted derivative (XL).

When chloroethyl oxalate, Cl-CO-COOEt, was allowed to react with β-aminocrotononitrile in pyridine, the C- derivative was formed. This C- derivative (XXXVI) reacted with two molecules of phenylhydrazine to yield water, ammonia, ethanol, and 1-phenyl-3-methyl-4-cyanopyrazole-5-carboxy-Nβ-phenylhydrazone (XLI).



(XLI)

The action of alkali upon (XLI) converted the cyano group into an acid which was identical with the acid obtained by the saponification of the product resulting from the action of phenylhydrazine upon



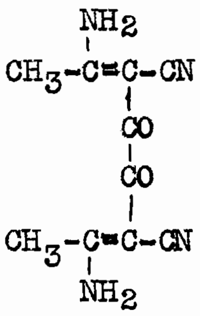
$$CH_3-\overset{NH_2}{C}=\underset{CO-COOEt}{C}-COOEt$$

The structure of (XLI) was verified readily by permanganate oxidation to 1-phenyl-3-methyl-4-cyanopyrazole-5-carboxylic acid, which was then saponified to the known 4,5-dicarboxylic acid.

Von Meyer (46) had condensed α-phenoxyethylacetate with β-aminocrotononitrile, and isolated two isomeric products. One of the products was α-phenoxyacetyl-β-aminocrotononitrile, and the other product was not identified further. Benary and Hosenfeld (8) investigated the action of both α-phenoxyethyl acetate and α-phenoxyacetyl chloride upon β-aminocrotononitrile. An anology was found between the oxalyl and phenoxyacetyl derivatives. The true C- derivatives were found to yield pyrazole compounds when heated at 100° for 20 minutes with three parts of phenylhydrazine. The N- derivatives either failed to react with the phenylhydrazine, or yielded C_6H_5-CO-NH-NH-C_6H_5 .

Cinnamoyl chloride, C_6H_5-CH=CH-COCl, was condensed with β-aminocrotononitrile to form both the N- and C- derivatives. Ethyl cinnamate condensed to yield the normal N- derivative.

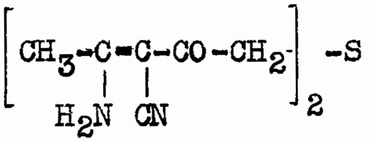
Benary, Soenderop and Bennewitz (14) isolated α-oxalylbis(β-aminocrotononitrile) (XLII) from the reaction of oxalyl


$$\begin{array}{c} NH_2 \\ | \\ CH_3-C=C-CN \\ | \\ CO \\ | \\ CO \\ | \\ CH_3-C=C-CN \\ | \\ NH_2 \end{array}$$

(XLII)

chloride and β-aminocrotononitrile.

The reaction of α-chloroacetyl chloride in ether with β-aminocrotononitrile in the presence of pyridine was studied by Benary and Lau (9), von Meyer (44), and Schwoch (56). The α-chloroacetyl-β-aminocrotononitrile, when treated with potassium hydrosulphide, yielded β-thiobis(α-acetyl-β-aminocrotononitrile) (XLIII). The chloroacetyl derivatives could be condensed to


$$\left[\begin{array}{c} CH_3-\underset{H_2N}{C}=\underset{CN}{C}-CO-CH_2- \end{array}\right]_2-S$$

pyrrole compounds by the action of alcoholic potash.

In 1951, Reynolds, Humphlett, Swamer and Hauser (51) reported the first reaction of β-aminocrotononitrile with Grignard reagents. They were investigating the preparation of

2-hydroxy-4-aminopyridines. β-Aminonitriles were condensed with an equimolecular quantity of Grignard reagent, and the magnesium derivatives were acylated with acid chlorides or anhydrides. The acyl derivatives were cyclized by sodium amide to form 2-hydroxy-4-aminopyridines. β-Aminocrotononitrile was acetylated in this manner in 62% yield. The N-acetyl derivative was treated with sodium amide, but the pyridine derivative was not obtained pure enough for analysis.

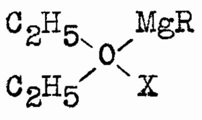
GRIGNARD REAGENTS AND REACTIONS

In 1900, Victor Grignard (30) discovered the formation of organomagnesium halides in the reaction of alkyl halides with metallic magnesium in ethyl ether solution, and demonstrated the extraordinary versatility of the new reagent in organic reactions.

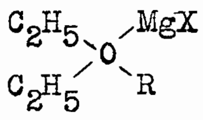
The earlier work on the Grignard reactions has been summarized by F. Runge in 1932 (52). In addition to that, the present thesis outlines the recent investigations and views on the structure and reaction mechanisms of Grignard reagents, with emphasis on the reaction with nitriles.

It has repeatedly been shown that the Grignard reagent is not a simple molecule made up of a magnesium atom, a halogen atom, and an organic radical. The usual representation of the Grignard reagent is R-Mg-X, but it does not tell the whole story of this versatile reagent.

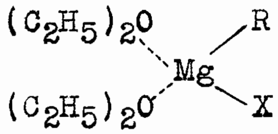
The formation of organomagnesium halides did not have to take place in ether. Spencer and his co-workers (58,59) reacted substituted alkyl halides and aryl chlorides directly with magnesium, and obtained crystalline compounds, which were decomposed by water to liberate the corresponding substituted hydrocarbon. This indicated that the RMgX was formed as the first step in the reaction, and that in ether solution the second step would be the association of the RMgX with the ether molecules. Grignard found that the organomagnesium compounds held at least one molecule of ether as 'ether of crystallization'. Tschelinzeff (62) concluded from measurements of heats of formation that there could be two or three molecules of ether associated with each RMgX molecule. The ether was assumed at this time to serve a dual role. It was not only the solvent, but acted as a catalyst by forming an additive compound with the alkyl halide, which subsequently reacted with the magnesium to form the alkyl magnesium halide, and regenerating the original ether. The structure of the associated molecule was not definitely established. Baeyer and Villiger (3) gave it the structure (XLIV). Grignard proposed structure (XLV) as the most likely structure. Meisenheimer (38) believed that the



(XLIV)



(XLV)



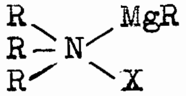
(XLVI)

properties of the complexes were best explained by assuming that the magnesium was the central atom, as in (XLVI). Jolibois (34,35) postulated the bimolecular formula (XLVII) for the etherate.

Tschelinzeff (62) found that the ether of the associated molecule could be replaced by tertiary amines, to form amine complexes, such as (XLVIII). This work was supported by Sachs and Sachs (53).

$R_2Mg, MgX_2, 2(C_2H_5)_2O$

(XLVII)



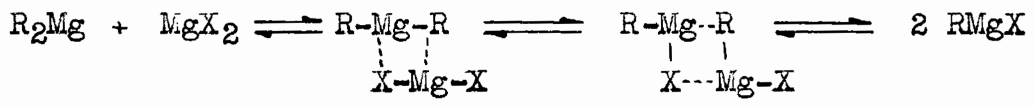
(XLVIII)

Pickard and Kenyon (50) obtained another complex of the type (XLIX), by the reaction of methyl magnesium iodide in

$$((C_7H_7)_3PO)_2 \cdots\cdots CH_3MgI \qquad \text{(XLIX)}$$

benzene with tribenzylphosphine oxide. It was also found that other ethers, such as di-n-butyl ether and di-n-amyl ether, could be used to form associated molecules.

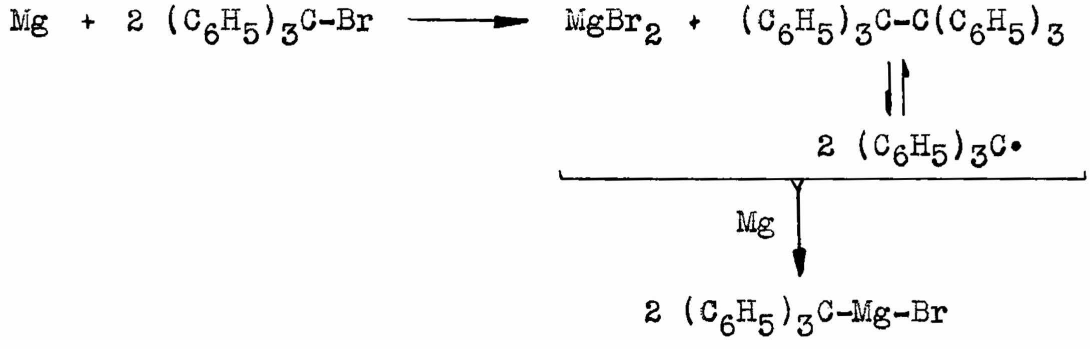
The fact that a Grignard reagent existed in equilibrium with a molecule of dialkyl or diaryl magnesium and magnesium halide had been known for a long time. Schlenk and Schlenk Jr.(54) had shown that the addition of dioxane to a solution of a Grignard reagent in ether would immediately precipitate the halogen-bearing portions, RMgX and MgX_2, leaving the R_2Mg in solution. The reaction of anhydrous zinc chloride with ethyl magnesium bromide in ether produced zinc diethyl immediately. By analogy, if magnesium halide were added to a solution containing R_2Mg, the exchange to RMgX would be instantaneous. It was difficult to postulate a purely ionic mechanism for such a rapid reaction in a solution of such low dielectric constant as ether, because the concentration of ions at any one time would be so small. The most likely mechanism involved a collision leading to an association of the highly polar molecules, followed by a dissociation, with the groups interchanged, as in the equation:



$$R_2Mg + MgX_2 \rightleftharpoons \begin{array}{c} R-Mg-R \\ \vdots \quad \vdots \\ X-Mg-X \end{array} \rightleftharpoons \begin{array}{c} R-Mg\cdots R \\ | \quad | \\ X\cdots Mg-X \end{array} \rightleftharpoons 2\ RMgX$$

Since the groups were lost and gained by the molecules with apparent ease, the immediate suggestion would be that primary ionic linkages were involved, and that the molecules could be considered as ionic pairs held together by coulombic forces. Gilman and Brown (28,29) showed that ether distillation of alkyl magnesium halides produced a distillate which contained the alkyl magnesium halide. This did not prove anything conclusively, because dialkyl magnesium and magnesium halide were also volatile under the same conditions. The ratio of magnesium to halogen was found to be almost one, as expected. The aryl magnesium halides did not distil under the same conditions.

Gomberg and Bachmann (2) observed that, when one mole of magnesium was added to two moles of triphenylmethyl bromide, no Grignard reagent was produced. The solution contained triphenyl methyl free radicals, which disappeared when the second mole of magnesium was added. The reaction could be outlined by the following equation:



$$\begin{array}{l} Mg + 2\ (C_6H_5)_3C-Br \longrightarrow MgBr_2 + (C_6H_5)_3C-C(C_6H_5)_3 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \Updownarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad 2\ (C_6H_5)_3C\cdot \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow{\scriptstyle Mg} \\ \qquad\qquad\qquad\qquad\qquad\qquad 2\ (C_6H_5)_3C-Mg-Br \end{array}$$

It can be shown that the free radicals were actually an intermediate stage in the preparation of triphenylmethylmagnesium bromide. When triphenyl-methyl carbinol was heated with a mixture of $MgBr_2$ and magnesium, and the reaction product was treated with water, there resulted a mixture of triphenylmethyl and triphenyl methane. The products were at first thought to arise from the following reactions:

$$(C_6H_5)_3C\text{-}OH + MgBr_2 \longrightarrow (C_6H_5)_3C\text{-}Br + Mg(OH)Br \qquad 1)$$

$$2\ (C_6H_5)_3C\text{-}Br + Mg \longrightarrow 2\ (C_6H_5)_3C\cdot + MgBr_2 \qquad 2)$$

$$(C_6H_5)_3C\text{-}Br \xrightarrow{Mg} (C_6H_5)_3CMgBr \xrightarrow{HOH} (C_6H_5)_3CH + Mg(OH)Br \qquad 3)$$

Reactions 2 and 3 were assumed to be in competition with each other. However, it was found that prolonged heating of the mixture decreased the yield of triphenylmethyl and increased the yield of the triphenylmethane, i.e. the free radical was just an intermediate stage in the formation of the Grignard reagent. In this manner, Bachmann and Gomberg showed that a Grignard reagent could be formed from a free radical and the binary system of magnesium and magnesium halide.

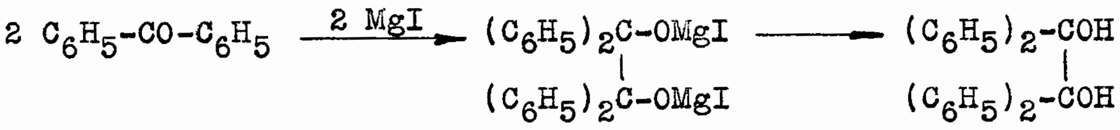
Gilman and Fothergill (27) followed up the work of Jolibois (34, 35) on the bimolecular formula, and attempted to reduce the question of the structure of the Grignard reagent to the simpler relationship:

$$2\ RMgX \rightleftharpoons R_2Mg,MgX_2$$

They set out to determine whether the magnesium halide was an integral part of the Grignard reagent by using the equilibrium,

$$MgI_2 + Mg \rightleftharpoons 2\ MgI$$

which had been successfully studued by Gomberg and Bachmann (1,2). It was known that the magnesious iodide would react with benzophenone to give the benzopinacol by the following path:



$$2\ C_6H_5\text{-}CO\text{-}C_6H_5 \xrightarrow{2\ MgI} \begin{matrix}(C_6H_5)_2C\text{-}OMgI\\ |\\ (C_6H_5)_2C\text{-}OMgI\end{matrix} \longrightarrow \begin{matrix}(C_6H_5)_2\text{-}COH\\ |\\ (C_6H_5)_2\text{-}COH\end{matrix}$$

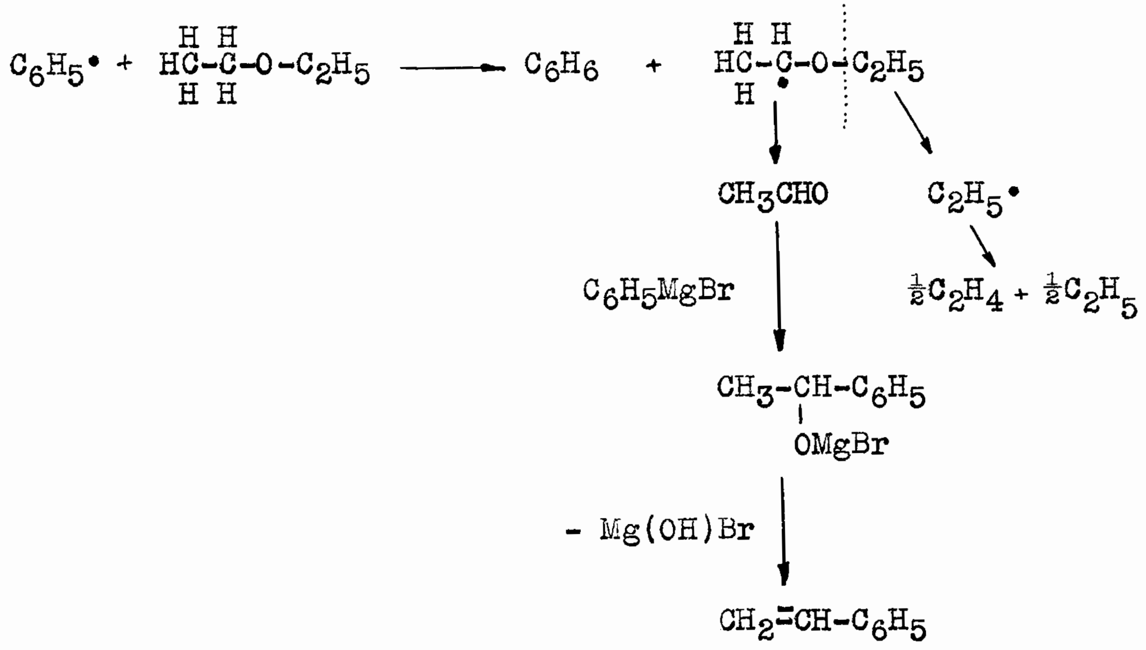
If the Grignard reagent had the dialkyl magnesium-magnesium halide structure, then the addition to the Grignard reagent of an equivalent of magnesium and two equivalents of benzophenone would result in the formation of equivalent quantities of benzopinacol and the tertiary alcohol formed by the reaction:

$$R_2Mg\ (\text{or}\ RMgX)\ +\ (C_6H_5)_2CO \longrightarrow R(C_6H_5)_2COH$$

When such an experiment was undertaken, very little benzopinacol was produced, indicating that the equilibrium of the system was shifted far to the side of RMgX. However, this equilibrium can be shifted to the other side by elevated temperatures, and by the addition of other solvents, such as dioxane.

The existence of free radicals in Grignard solutions has been shown in other ways. The electrolysis of aliphatic Grignard reagents in ether produced alkyl free radicals, which then would react further (1) by coupling, (2) by disproportionation, and (3) by removal of hydrogen from the solvent. Aromatic Grignard reagents behaved in a somewhat similar manner, to produce aryl free radicals, which generally reacted further by removal of hydrogen from the solvent. Evans, Pearson and Braithwaite (24) investigated the electrolysis of phenyl magnesium bromide, and identified the chief products as styrene, ethanol, ethane, ethylene, and terphenyl. The first four products were undoubtedly formed by the attack of the free radicals upon the solvent molecules. Evans and Field have proposed a mechanism for such an attack. Either an α- or a β-hydrogen can be removed from the ether by the free radical, by the following reactions:

a)

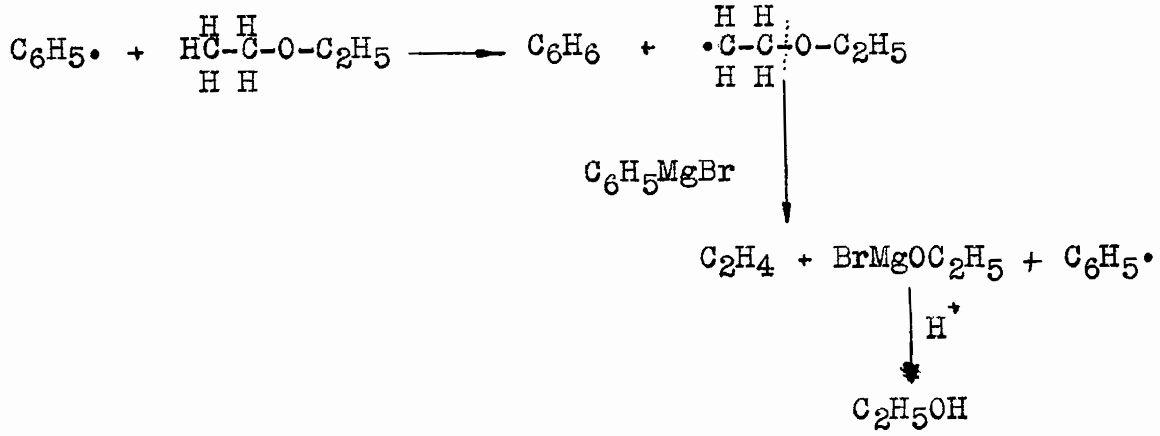


$$C_6H_5\cdot + H\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-C_2H_5 \longrightarrow C_6H_6 + H\underset{H}{C}-\overset{H}{\underset{\cdot}{C}}-O-C_2H_5$$

$$CH_3CHO \xrightarrow{C_6H_5MgBr} CH_3-\underset{OMgBr}{CH}-C_6H_5 \xrightarrow{-\ Mg(OH)Br} CH_2=CH-C_6H_5$$

$$C_2H_5\cdot \longrightarrow \tfrac{1}{2}C_2H_4 + \tfrac{1}{2}C_2H_5$$

b)



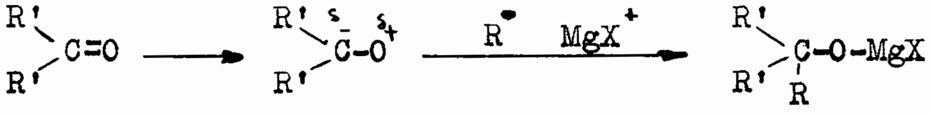
$$C_6H_5\cdot + H\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-C_2H_5 \longrightarrow C_6H_6 + \cdot\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-C_2H_5$$

$$\xrightarrow{C_6H_5MgBr} C_2H_4 + BrMgOC_2H_5 + C_6H_5\cdot$$

$$BrMgOC_2H_5 \xrightarrow{H^+} C_2H_5OH$$

This reaction with the hydrogen atoms of the solvent molecules has not been met with in very many investigations. In the electrolysis of some aliphatic Grignard reagents, the secondary alcohols formed by the action of the excess Grignard reagent with the acetaldehyde had been found. Phenyl methyl carbinol might have been produced instead of the styrene, but Klages had shown that excess Grignard reagents could act as dehydrating agents for the magnesium salts of secondary and tertiary alcohols. Some coupling of the free radicals produced by the electrolysis of phenyl magnesium bromide did take place to form biphenyl. The biphenyl acted as a ready source of hydrogen atoms for other phenyl free radicals, so that biphenyl free radicals were formed. These radicals coupled with other free phenyl radicals to form terphenyl. This process was repeated until an insoluble, high melting solid was produced. Such a solid was actually found by Evans, Pearson and Braithwaite.

In a number of reactions, the Grignard reagent appeared to react as an R^- anion and a MgX^+ cation. When reacting with a compound containing a polar group, such as a carbonyl group, the anion with its unshared pair of electrons went to the atom with the open sextet, and the cation added to the atom with an unshared pair of electrons. The reaction with a ketone could be represented by the following reaction:



If an atom with an open sextet were not present, an ionizable hydrogen atom might furnish the necessary orbital for the unshared pair of electrons of the anion. This hydrogen atom could come from an OH, NH, SH, or an active methylene grouping. In some cases, as in the reaction with the allyl bromide molecule, the R anion behaved like any other anion, displacing the bromide ion by the usual displacement reaction. These reactions were all irreversible because of the stability of the C-C and C-H bonds formed during the reactions.

The electrolysis of various Grignard reagents was carried out by Evans and Pearson (23). The products were found to be magnesium metal at the cathode, various hydrocarbons at the anode, and magnesium halide in the solution. Several equations were suggested as representing the electrode reactions. They were the following:

a) at the cathode: $Mg^{++} + 2e \longrightarrow Mg$
at the anode: $R_2MgX_2^{=} - 2e \longrightarrow 2\,R\cdot + MgX_2$

b) at the cathode: $2\,RMg^{+} + 2e \longrightarrow Mg + R_2Mg$
at the anode: $2\,RMgX_2^{-} - 2e \longrightarrow 2\,R\cdot + 2\,MgX_2$

However, it is clear that we are not dealing with simple free anions. A Grignard reagent will carry a current, but it has also been found that magnesium has been isolated in the anion, as well as in the cation. There are, in addition, more equivalents of R plus X transferred to the anode than there are faradays of electricity used. Evans and Pearson showed that the molar conductance of a Grignard reagent increased with concentration, this being the reverse of the usual ionization phenomenon of molar conductance decreasing with concentration. The ions were complex ions built up of ether molecules, RMgX, R_2Mg, and MgX_2. The ether molecule was strictly an electron donor by virtue of the unshared pair of electrons on the oxygen atom. Similarly, RMgX and MgX_2 were donor molecules by virtue of the unshared electron pairs of the halogen atoms. RMgX, MgX_2 and R_2Mg were electron acceptor molecules, because of the two stable unfilled orbitals of the magnesium atoms.

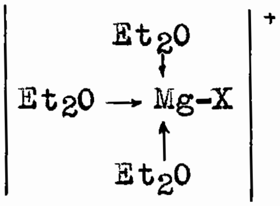
The following ionic ruptures were all quite likely.

$$RMgX \longrightarrow R^- + MgX^+ \quad \text{or} \quad X^- + MgR^+$$

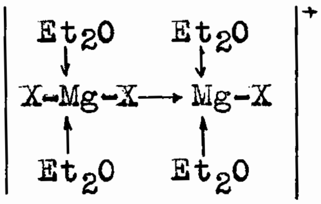
$$R_2Mg \longrightarrow R^- + RMg^+$$

$$MgX_2 \longrightarrow X^- + MgX^+$$

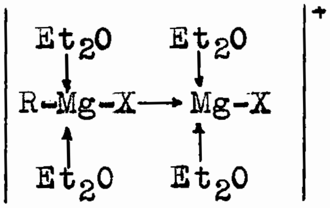
The MgX^+ cation has three stable unfilled orbitals, so it can be very highly solvated. This high solvation decreased the mobility of the cation, in agreement with transference data which indicated a large transference of matter to the anode. There were several solvated cations suggested by Evans, as follows:



$$\left| Et_2O \rightarrow \underset{\underset{Et_2O}{\uparrow}}{\overset{\overset{Et_2O}{\downarrow}}{Mg}}{-}X \right|^+$$

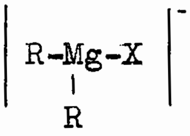


$$\left| X{-}\underset{\underset{Et_2O}{\uparrow}}{\overset{\overset{Et_2O}{\downarrow}}{Mg}}{-}X \longrightarrow \underset{\underset{Et_2O}{\uparrow}}{\overset{\overset{Et_2O}{\downarrow}}{Mg}}{-}X \right|^+$$

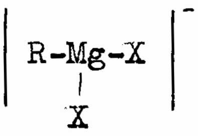


$$\left| R{-}\underset{\underset{Et_2O}{\uparrow}}{\overset{\overset{Et_2O}{\downarrow}}{Mg}}{-}X \longrightarrow \underset{\underset{Et_2O}{\uparrow}}{\overset{\overset{Et_2O}{\downarrow}}{Mg}}{-}X \right|^+$$

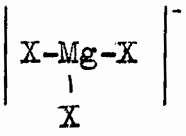
The anions contained an unshared electron pair, and therefore were only weakly attracted to ether molecules. Consequently, they would coordinate with acceptor molecules containing the magnesium ion, giving such anions as the following:



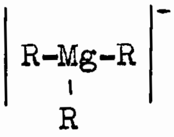
$$\left| R{-}\underset{\underset{R}{|}}{Mg}{-}X \right|^-$$



$$\left| R{-}\underset{\underset{X}{|}}{Mg}{-}X \right|^-$$



$$\left| X{-}\underset{\underset{X}{|}}{Mg}{-}X \right|^-$$



$$\left| R{-}\underset{\underset{R}{|}}{Mg}{-}R \right|^-$$

The negative charge made the anion a stronger base than the ether molecules, and displaced the ether molecules from other magnesium atoms, building up large mobile anions. When butyl magnesium bromide was electrolysed, more R was transferred to the anode than X. This was probably due to the R_2Mg being a better electron acceptor than MgX_2, and associating with the anions more readily.

At the electrodes, various possibilities of discharge arose. The cation might be discharged to give $RMg\bullet$ or $MgX\bullet$ free radicals, which then reacted in pairs to give magnesium and R_2Mg or MgX_2.

$$2\ RMg\overset{+}{\bullet} + 2e \longrightarrow R_2Mg + Mg$$
$$2\ MgX\overset{+}{\bullet} + 2e \longrightarrow MgX_2 + Mg$$

The anion would be discharged in such a way that the group having the lowest discharge potential would be liberated as a free radical or atom. For aliphatic Grignard reagents, or aromatic Grignard reagents at low current density, the R groups were the most readily discharged group.

$$R_2Mg\overline{X} \longrightarrow R\bullet + RMgX + e$$
$$MgR_3^- \longrightarrow R\bullet + R_2Mg + e$$
$$RMgX_2^- \longrightarrow R\bullet + MgX_2 + e$$

Under certain circumstances, the halide ion might be discharged preferentially.

$$RMgX_2^- \longrightarrow X\bullet + RMgX + e$$
$$R_2MgX^- \longrightarrow X\bullet + R_2Mg + e$$
$$MgX_3^- \longrightarrow X\bullet + MgX_2 + e$$

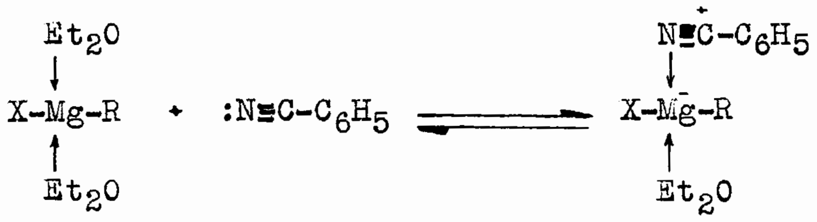
The following reactions could then occur:

$$2\ X\bullet \longrightarrow X_2$$
$$X_2 + RMgX \longrightarrow RX + MgX_2$$
$$RX + Mg \longrightarrow RMgX$$

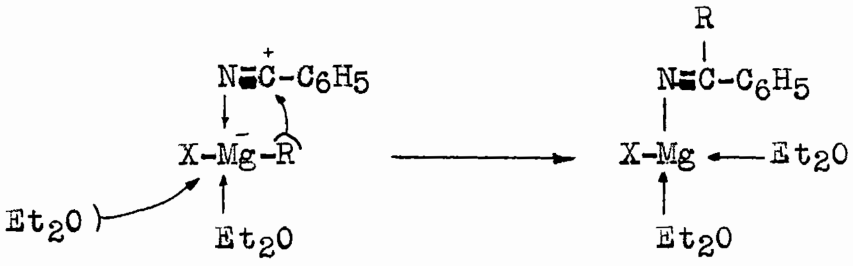
As support for these latter reactions, several reactions could be cited. The electrolysis of aliphatic Grignard reagents generally produced a gray crystalline type of magnesium at the cathode with almost 100% efficiency. The electrolysis of phenyl magnesium bromide proceeded at reduced current efficiency to yield a black powdery type of magnesium at the cathode. Bromobenzene was isolated from the solution. It was this bromobenzene which diffused to the cathode, and reacted with the deposited magnesium, accounting for its appearance. To show the existence of the halogen molecule intermediate, Evans and Pearson (23) electrolysed phenethynylmagnesium iodide to the iodide ion, which collected on the anode as a mass of crystalline iodine. Iodine was known to react only very slowly with phenethynylmagnesium iodide. Such discharge of halide ion was favored by the high electronegativity of the radical, the low electronegativity of the halogen, and by high voltages. Aryl radicals were more electronegative than alkyl radicals, with the result that electrolysis of aromatic Grignard reagents had a low current efficiency.

The necessity of having both electron donor and electron acceptor molecules to promote ionization in solvents of low dielectric constant could be shown quite simply. Zinc or magnesium diethyl, which were conductors in ether, were non-conductors in benzene solution. That was because the benzene had poor electron donor properties. Magnesium bromide and ethyl magnesium bromide in benzene were fairly good conductors, by virtue of the electron donor properties of the halogen atoms. Zinc diethyl itself was a non-conductor, but its solution in ether would conduct electric current, because of the solvation of the $ZnEt^+$ cation.

The kinetics of the Grignard reaction with nitriles was studied by Swain (61), who found the free carbanion conception was an oversimplification. The reaction between n-butylmagnesium bromide and benzonitrile was strictly a second order reaction. This eliminated any mechanism involving a unimolecular or solvolytic ionization of the Grignard reagent to a carbanion as the rate determining step. Swain proposed a mechanism which was consistant with the kinetic order, and all reported series of relative reactivity. A complex was formed between the reagent and the addend in a rapid and reversible manner, probably in very low concentration compared to the reagent concentration. This complex involved the displacement of a solvating ether molecule from the RMgX.2Et$_2$O by the free electron pair of the nitrile group, as in the following equation:

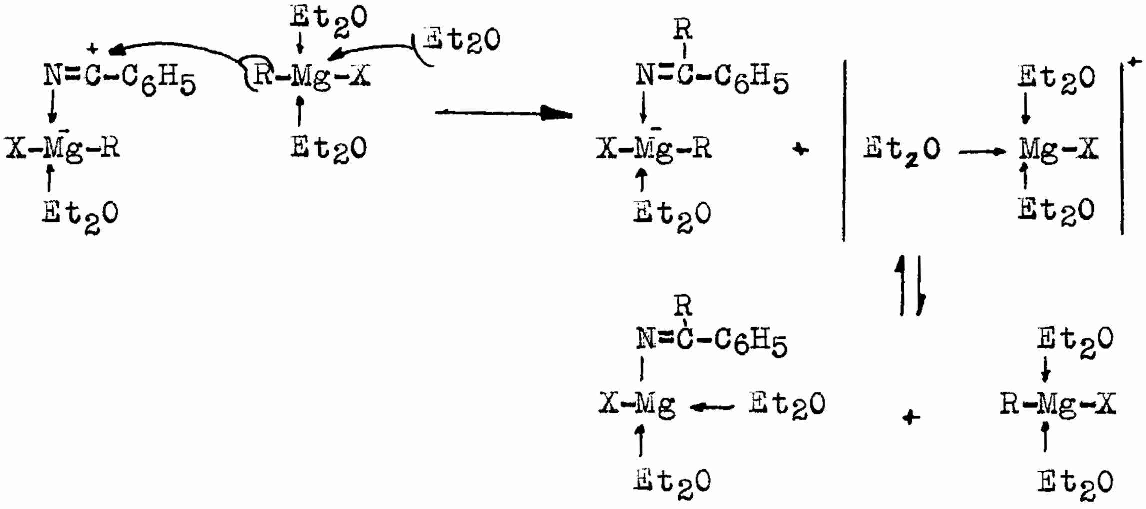


The reaction could then proceed by the rate determining step of the intramolecular rearrangement of the alkyl group attached to the magnesium, together with its pair of electrons, to the positive carbon atom of the nitrile group.



An intermolecular reaction of the complex with another molecule of

Grignard reagent, as in the following reaction, appeared to be



eliminated, because it would require second order kinetics in the reagent alone, and third order kinetics over all.

The relative reactivity of Grignard reagents with benzonitrile was found to be

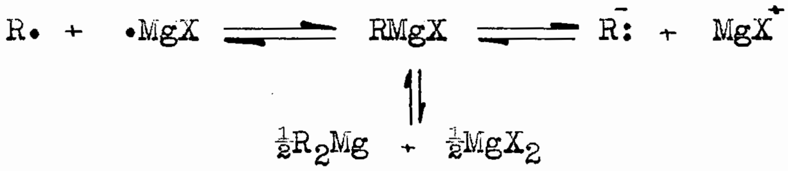
p-tolyl or α-naphthyl $>$ phenyl $>$ p-chlorophenyl $>$ methyl.

This order of relative reactivity was the same as the migration aptitudes of the radicals in the pinacol rearrangement, which was believed to be a similar intramolecular shift of the radical with its electron pair.

In some Grignard reactions, an intermolecular path may be justified. The order of reaction of Grignard reagents with benzophenone was the reverse of the order of reactivity with benzonitrile. With an equivalent amount of Grignard reagent, benzophenone rapidly formed a precipitate, from which benzophenone may be liberated by the addition of water. Addition of excess Grignard reagent to the precipitate caused it to dissolve, and the reaction proceeded to completion. This was a case of excess

Grignard reagent reacting with a molecule of benzophenone already polarized by complex formation. The complex was stable toward internal rearrangement, because it was a precipitate.

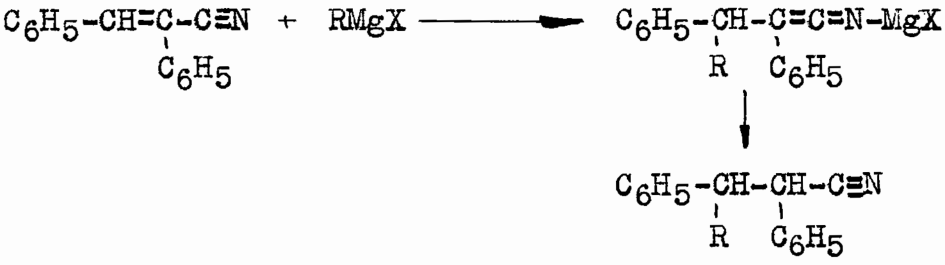
The structure and reaction mechanisms of Grignard reagents is quite complex, and any simple representation would of necessity be inadequate. However, it can be said, in summing up, that in most Grignard reactions, the reagent dissociated rapidly and reversibly into carbanions, dialkyl or diaryl magnesium compounds, and into free radicals.



$$\begin{tikzcd} R\cdot + \cdot MgX \arrow[r, shift left] & RMgX \arrow[l, shift left] \arrow[r, shift left] \arrow[d, shift left] & \overset{-}{R:} + MgX^{+} \arrow[l, shift left] \\ & \tfrac{1}{2}R_2Mg + \tfrac{1}{2}MgX_2 \arrow[u, shift left] & \end{tikzcd}$$

The usual representation of a Grignard reaction indicates the end result, and not the path to that result.

Unsaturated nitriles, having the carbon-carbon double bond conjugated with the triple bond of the cyano group, and having a substituent in the α-position, were found to react with Grignard reagents to form α-substituted saturated nitriles, by a 1,4-addition mechanism. The reaction could be represented by the following:



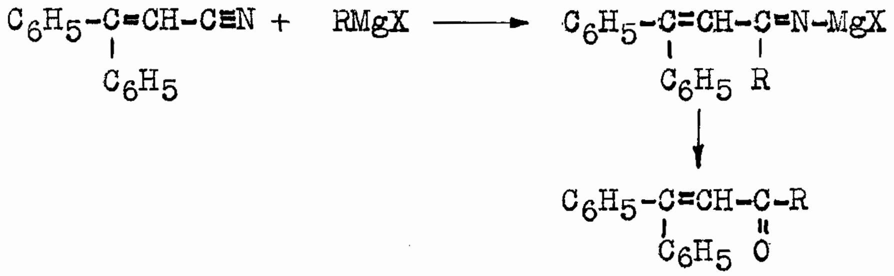
$$C_6H_5\text{-}CH{=}\underset{C_6H_5}{C}\text{-}C{\equiv}N + RMgX \longrightarrow C_6H_5\text{-}\underset{R}{CH}\text{-}\underset{C_6H_5}{C}{=}C{=}N\text{-}MgX$$

$$\downarrow$$

$$C_6H_5\text{-}\underset{R}{CH}\text{-}\underset{C_6H_5}{CH}\text{-}C{\equiv}N$$

If the nitrile was substituted in the β-position, the reaction with

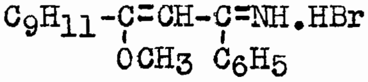
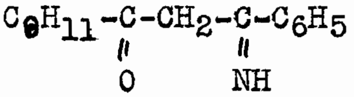
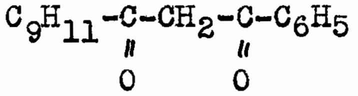
Grignard reagents produced an unsaturated ketone in the usual manner, as represented by the following:



$$C_6H_5-\underset{\substack{|\\ C_6H_5}}{C}=CH-C\equiv N + RMgX \longrightarrow C_6H_5-\underset{\substack{|\\ C_6H_5}}{C}=CH-\underset{\substack{|\\ R}}{C}=N-MgX$$

$$\downarrow$$

$$C_6H_5-\underset{\substack{|\\ C_6H_5}}{C}=CH-\underset{\substack{\|\\ O}}{C}-R$$

An example of this reaction would be the reaction of β-methoxy-β-mesitylacrylonitrile with phenyl magnesium bromide. The products were the imino bromide,  $C_9H_{11}-\underset{\substack{|\\ OCH_3}}{C}=CH-\underset{\substack{|\\ C_6H_5}}{C}=NH.HBr$, an imino ketone,  $C_9H_{11}-\underset{\substack{\|\\ O}}{C}-CH_2-\underset{\substack{\|\\ NH}}{C}-C_6H_5$, and the diketone,  $C_9H_{11}-\underset{\substack{\|\\ O}}{C}-CH_2-\underset{\substack{\|\\ O}}{C}-C_6H_5$.

DISCUSSION OF RESULTS

From the time of its discovery in 1889, β-aminocrotononitrile has been the subject of a number of papers, none of which have seriously considered the structure of the two crystalline modifications of the compound. The object of the present work was to investigate the structure of the two modifications by various physical and chemical means. An investigation was also undertaken to determine the products of bromination of β-aminocrotononitrile, and the products from the reaction of aromatic Grignard reagents in excess with β-aminocrotononitrile.

The preparation of the two modifications was readily accomplished by the procedure developed by Holtzwart (32). The immediate products of the reaction between three moles of acetonitrile and two moles of metallic sodium were a gas and a white crystalline precipitate. The gas had been previously identified by von Meyer (40) as methane. The crystalline precipitate was a mixture of sodium cyanide and the sodium salt of β-aminocrotononitrile. The decomposition of the sodium salt was the key step in the isolation of the two modifications. The low melting modification was obtained in good yield when the sodium salt was decomposed with warm (30-35°) water, and then extracted with ethyl ether. Removal of the ether yielded crystalline β-aminocrotononitrile, which could be recrystallized from benzene as fine needles, melting at 52-53°C. The high melting modification was obtained in good yield when the sodium salt was suspended in ether, cooled in ice water, and decomposed with ice water. The ether extract, when the ether was removed, yielded the crystalline β-aminocrotononitrile, which could be recrystallized from warm (50°) benzene as long white needles, melting at 79-83°C. after several recrystallizations. The mother liquors from the crystallization of the high melting modification yielded the low melting modification, when the solvent was evaporated. The high melting modification was converted quantitatively into the low melting form by fusion, and recrystallization of the fused melt from benzene. The solubilities of the two modifications in benzene were found by von Meyer (42) to be quite different. The solubility of the low melting form was 8.57 gm./ 100 gm. of benzene at 16.5°C. The solubility of the high melting form was 1.22 gm./ 100 gm. of benzene at 16.5°C.

The reactions of the two modifications were found to be identical. Both modifications reacted with aniline in glacial acetic acid to produce β-phenylaminocrotononitrile (page 14) in 90% yields. Both modifications were brominated with a solution of bromine in 10% potassium bromide solution to produce β-bromoaminocrotononitrile in 20% yields. The irradiation of an ethanol solution of the low melting modification with ultraviolet light did not change the original low melting modification. The ultraviolet absorption spectra were taken for solutions of both modifications in absolute ethanol, acetonitrile, and cyclohexane. The absorption range from 220 to 295 millimicrons was investigated, and the molar extinction coefficients were plotted against the wavelength of the ultraviolet light. The wavelengths and the molar extinction coefficients of the observed maxima of the curves are listed in Table II.

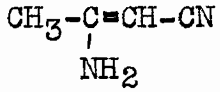
In all cases, except one, the absorption curves were smooth symmetrical curves, with only one well defined maximum on each curve. The one exception was the curve obtained for the solution of the high melting modification in dry cyclohexane. In addition to the usual maximum, there appeared to be a masking band extending from 220 millimicrons toward the lower wavelengths. Such a band was not found for the low melting modification in cyclohexane. This band had an optical density of .048, as compared to an optical density of .099 for the maximum. No values of the molar extinction coefficients were obtained for the cyclohexane solutions, because of the difficulty in determining the concentrations of the solutions, due to the extremely low solubility of the solute. It was found that, in the polar solvents, the maxima occurred at the same wavelength for both modifications. This indicated that both modifications had similar electronic configurations when dissolved in polar solvents. In the non-polar solvent, the maxima for the two modifications were quite different. The maximum for the low melting modification occurred at 250 millimicrons, and for the

TABLE II.

Wavelengths and Molar Extinction Coefficients of Observed Maxima of Ultraviolet Absorption Spectra.

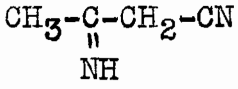
Solvent	Absolute Ethanol		Acetonitrile		Cyclohexane	
	λ max	ϵ max	λ max	ϵ max	λ max	ϵ max
Low Melting Modification	258 mμ	13,600	254.5 mμ	12,430	250 mμ	-
High Melting Modification	258 mμ	14,700	254.5 mμ	13,650	244 mμ	-

high melting modification the maximum was found at 244 millimicrons, indicating that the two modifications did not have quite the same electronic configuration when dissolved in non-polar solvents. It has been reported by Braude (16) that the maximum for acrylonitrile occurred at 250 millimicrons with a molar extinction coefficient of 5. The observed ultraviolet absorption spectra of β-aminocrotononitrile could be explained if β-aminocrotononitrile were considered as a derivative of acrylonitrile, rather than as a derivative of butyronitrile, which has its maximum well below 180 millimicrons. An isolated cyano group would produce a maximum near 160 millimicrons. The acrylonitrile has the cyano group conjugated with the double bond in the side chain of the molecule. The maximum of the absorption spectrum of acrylonitrile would be shifted to the higher wavelength region if the molecule were substituted by any group containing unsaturated bonds or unshared electron pairs which could be conjugated with the conjugated bond system of the acrylonitrile. In addition, if resonance were possible in the substituted acrylonitrile molecule, the molar extinction coefficient would be greatly increased. One of the first possibilities for isomeric structures of β-aminocrotononitrile is that the hydrogen atoms of the methylene group adjacent to the cyano group are labile, and shift to the nitrogen of the imino group in the β-position of the β-iminobutyronitrile. This type of a shift would be analogous to the enolization of a ketone. The two tautomers are represented by the following structures.



$$\mathrm{CH_3-\underset{NH_2}{\underset{|}{C}}=CH-CN}$$

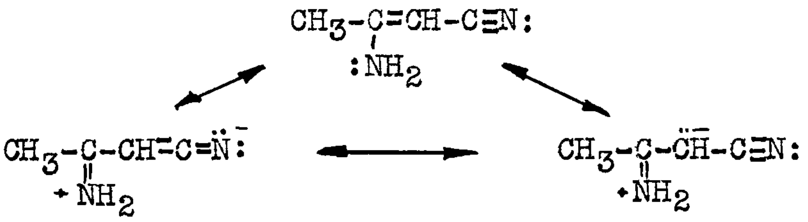
Enamine Type



$$\mathrm{CH_3-\underset{NH}{\underset{\|}{C}}-CH_2-CN}$$

Ketimine Type

From the ultraviolet absorption data on β-aminocrotononitrile, it is evident that, at least in solution, the enamine type of structure is present rather than the ketimine type. The author now advances a new and more detailed explanation of the structure of β-aminocrotononitrile based on the modern concepts of theoretical organic chemistry. The unshared electron pair of the amino nitrogen atom acts as a conjugated chromophoric group, shifting the absorption maximum toward the higher wavelengths. There is the possibility that the enamine form of β-aminocrotononitrile exists as a resonance hybrid of three resonating structures, whereas the ketimine type could not resonate. Two structures of the resonating hybrid are ionic, as represented in the following scheme:



This resonance would account for the high molar extinction coefficients that were determined.

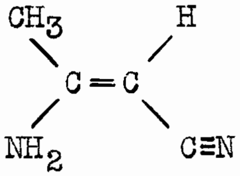
It is known* that in an ideal solution, the heat of solution of a solid is identical with its heat of melting at the same temperature. Rough values for the heats of fusion of the two modifications of β-aminocrotononitrile are therefore given by the heats of solution of the two modifications in benzene, assuming ideal conditions for the solutions. Knowing the melting points of the two modifications, and their solubilities at 16.5°C., it is

*Steiner, L. 'Introduction To Chemical Thermodynamics', McGraw-Hill Book Company, Inc., Second Edition, Page 288.

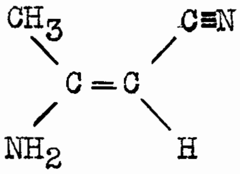
possible to obtain the solubility curves for the two modifications. The plot of the logarithm of the mole fraction versus the inverse of the absolute temperature was a straight line plot. The heats of solution were obtained by multiplying the intercept by the term- 2.303RT. It is found that the values of the heats of solution of the two modifications, at the melting point, are identical within experimental limits of error. It is quite safe to assume that the heats of fusion of the two modifications will be of the same order of magnitude, and almost identical to each other. The heats of fusion of enamine and ketimine tautomers would not be identical, with the result that such tautomers are ruled out as possible structures for the two modifications of β-aminocrotononitrile.

Polymorphism has been observed among organic compounds in a large number of cases. The possibility of the two modifications being polymorphic modifications has been investigated. Enantiotropic polymorphism demanded the existence of a transition temperature, above which one modification would be stable and the other modification would be metastable, and below which the order of metastability would be reversed. This meant that the two forms should be entirely interconvertible at some temperature below their melting points. Also, there should be only one melting point for the compound. No such transition temperature has been found for β-aminocrotononitrile, the lower melting modification being the stable modification at all temperatures. Both forms had definite melting points. These lines of evidence ruled out the existence of enantiotropic polymorphism. Monotropic polymorphism appeared to be a likely possibility at first. Such polymorphism demanded the existence of an imaginary transition temperature, that is, one which was above the melting points of the two modifications. One modification would be stable, and the other one would be metastable at all times. There would be two melting points, one for each modification. Such stability, and the two melting points were found in the case of β-aminocrotononitrile. However, the order of stability is the reverse of the expected order. The lower melting modification, if it is a polymorph of the monotropic type, should be the metastable form, and should spontaneously transform into the higher melting modification. Investigations have shown that the low melting modification is the more stable of the two modifications, and that the direction of transformation is from the high melting form to the low melting form. In addition, the heats of fusion of polymorphic modifications have been found to differ greatly. Because the heats of fusion of the two modifications of β-aminocrotononitrile were found to be nearly identical, the existence of polymorphism has been ruled out.

The ultraviolet absorption studies have indicated an enamine type of structure for β-aminocrotononitrile in solution. There is the possibility of cis-trans isomerism about the double bond. This would produce the two isomers represented by the

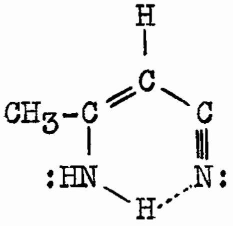


CIS (L)



TRANS (LI)

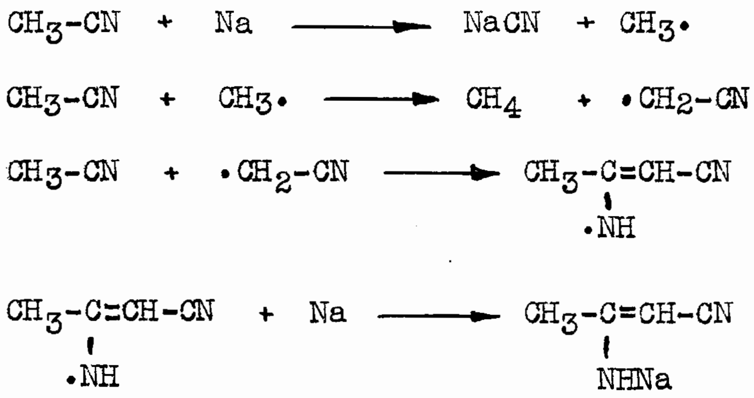
structures (L) and (LI). It is now proposed, as a result of the present investigations, that the two modifications of β-aminocrotononitrile are cis and trans isomers. The high melting form has been given the trans structure (LI) by virtue of its higher melting point and lower solubility. The low melting form has been given the cis structure (L) by virtue of its lower melting point and higher solubility. There is no possibility of internal hydrogen bonding in the trans form, because the amino and cyano groups are not in adjacent positions. However, in the cis form, the amino group and the cyano group are in adjacent positions, and can form an internal hydrogen bond, as in structure (LII).


(LII)

This hydrogen bond would stabilize the molecule to a certain extent. It is this stabilization which makes the cis form more stable than the trans isomer. This meant that irradiation of the lower melting modification with ultraviolet light would not cause any transformation of the molecule into the trans isomer. There are additional ionic structures (see page 42) which could influence the physical properties of the molecule. β-Aminocrotononitrile very readily crystallized in both modifications from a non-polar solvent, like benzene. However, crystallization of both modifications from a polar solvent, like ethanol, produced only the low melting cis modification. The explanation for this behavior lies in these ionic structures. In polar solvents, the contribution of the ionic structures to the final resonance hybrid would be greater than in a non-polar solvent. These ionic structures do not possess the double bond of the enamine system, permitting the free rotation about the single bond between the α- and β- carbon atoms. The final configuration of the molecule would be expected to be the stable one, which is the cis configuration stabilized by internal hydrogen bonding. This contention is upheld by the fact that crystallization of the high melting modification from ethanol converted it into the low melting modification. The contribution of the ionic structures to the final system in a non-polar solvent would be small, with the main contribution coming from the enamine structure. Thus, the cis-trans configurations would be maintained in a non-polar solvent, permitting the recrystallization of both modifications unchanged from benzene.

MECHANISM OF FORMATION OF β-AMINOCROTONONITRILE.

The Holtzwart (1889) mechanism of the reaction of acetonitrile with sodium leaves much to be desired. The decomposition of acetonitrile by two paths, resulting in the formation of sodium cyanide and a free methyl group by one path, and sodiumacetonitrile and a free hydrogen atom by the other path, seems quite improbable. One path, namely the path producing sodium cyanide, appears necessary to account for the presence of sodium cyanide in the final product. A free radical mechanism is now proposed, using the free methyl radical released in the primary decomposition. The reaction is represented by the following equations.



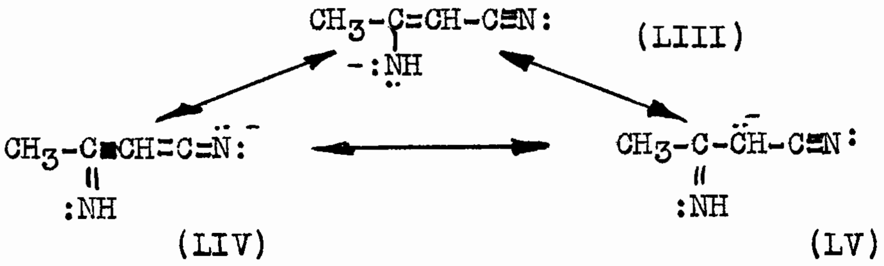
$$CH_3\text{-}CN + Na \longrightarrow NaCN + CH_3\cdot$$

$$CH_3\text{-}CN + CH_3\cdot \longrightarrow CH_4 + \cdot CH_2\text{-}CN$$

$$CH_3\text{-}CN + \cdot CH_2\text{-}CN \longrightarrow CH_3\text{-}\underset{\underset{\cdot NH}{|}}{C}{=}CH\text{-}CN$$

$$CH_3\text{-}\underset{\underset{\cdot NH}{|}}{C}{=}CH\text{-}CN + Na \longrightarrow CH_3\text{-}\underset{\underset{NHNa}{|}}{C}{=}CH\text{-}CN$$

The free methyl radical extracts a hydrogen atom from the second molecule of acetonitrile, forming methane and the free $\cdot CH_2\text{-}CN$ radical. This radical attacks the third molecule of acetonitrile to form the free β-aminocrotononitrile anion, which reacted with the second atom of sodium to produce the sodium salt of β-aminocrotononitrile. It is likely that the sodium salt is not quite as simple as described above. The β-aminocrotononitrile anion is capable of existing as the resonance hybrid of three



(LIII)

$$CH_3\text{-}\underset{\underset{-:\ddot{N}H}{|}}{C}{=}CH\text{-}C{\equiv}N:$$

(LIV)

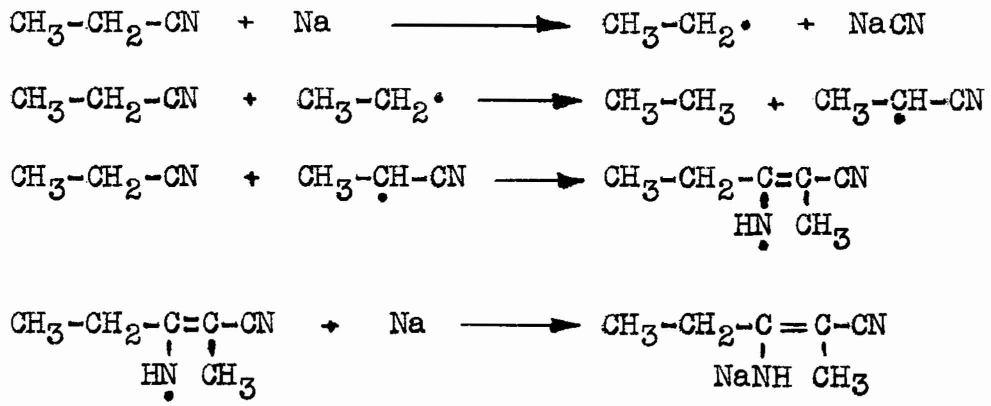
$$CH_3\text{-}\underset{\underset{:NH}{\|}}{C}\text{-}CH{=}C{=}\ddot{N}:^-$$

(LV)

$$CH_3\text{-}\underset{\underset{:NH}{\|}}{C}\text{-}\overset{-}{\ddot{C}}H\text{-}C{\equiv}N:$$

resonating structures, (LIII,LIV, and LV).

This mechanism could apply equally well to the reaction of other alkyl cyanides, such as propionitrile, with sodium. The reaction of three molecules of propionitrile with two molecules of sodium produced α-methyl-β-iminovaleronitrile in 71% yield. The mechanism for this reaction would be represented by the following equations.



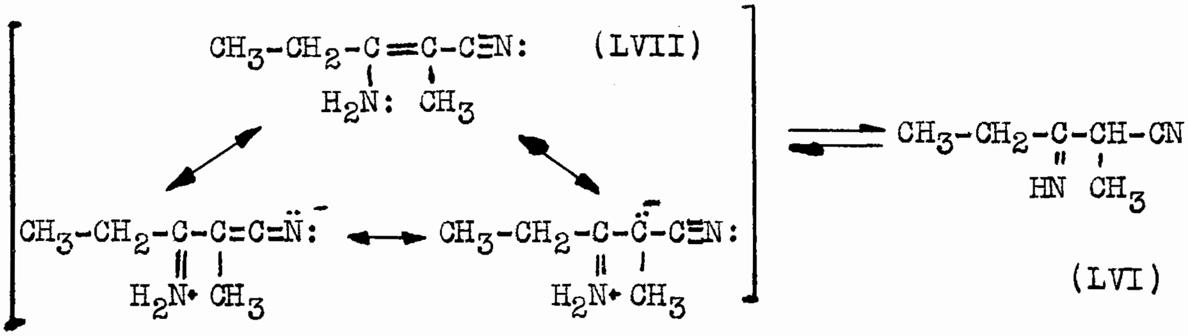
$$CH_3\text{-}CH_2\text{-}CN + Na \longrightarrow CH_3\text{-}CH_2\bullet + NaCN$$

$$CH_3\text{-}CH_2\text{-}CN + CH_3\text{-}CH_2\bullet \longrightarrow CH_3\text{-}CH_3 + CH_3\text{-}\underset{\bullet}{C}H\text{-}CN$$

$$CH_3\text{-}CH_2\text{-}CN + CH_3\text{-}\underset{\bullet}{C}H\text{-}CN \longrightarrow CH_3\text{-}CH_2\text{-}\underset{H\underset{\bullet}{N}}{\underset{|}{C}}{=}\underset{CH_3}{\underset{|}{C}}\text{-}CN$$

$$CH_3\text{-}CH_2\text{-}\underset{H\underset{\bullet}{N}}{\underset{|}{C}}{=}\underset{CH_3}{\underset{|}{C}}\text{-}CN + Na \longrightarrow CH_3\text{-}CH_2\text{-}\underset{NaNH}{\underset{|}{C}}{=}\underset{CH_3}{\underset{|}{C}}\text{-}CN$$

There was no evidence that the free ethyl radicals disproportionated into ethane and ethylene. The gas produced by the reaction was washed with aqueous bromine solution without the formation of ethylene dibromide. The α-methyl-β-iminovaleronitrile was also capable of existing in tautomeric ketimine (LVI) and enamine (LVII) structures, the latter being stabilized by resonance.

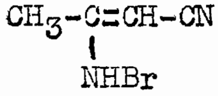


The α-methyl-β-iminovaleronitrile anion is capable of resonance in a manner similar to the resonance of the β-aminocrotononitrile anion.

α-Methyl-β-iminovaleronitrile is obtained by the decomposition of the sodium salt with water, and distillation of the dried ether extract under reduced pressure. It was an oil, which crystallized incompletely to flat plates, melting at 44-45°C. No further investigations of the structure of the molecule were carried out.

BROMINATION OF β-AMINOCROTONONITRILE

Von Meyer (42,43) prepared β-bromoaminocrotononitrile (LVIII) by the reaction of β-aminocrotononitrile with bromine in caustic potash, and with cyanogen bromide in benzene.



$$\underset{\displaystyle NHBr}{CH_3-\underset{|}{C}=CH-CN}$$

(LVIII)

The present investigation has shown that β-aminocrotononitrile can be brominated readily in aqueous solution by a solution of bromine in 10% potassium bromide solution. The yields are found to be low: 10-15% of theory. The monobromo compound that is obtained has the same melting point, 122-123°C., as that found by von Meyer. The direct bromination of β-aminocrotononitrile in benzene and in glacial acetic acid resulted in very poor yields of the monobromo compound. The yields were 10% and 5% in benzene and glacial acetic acid respectively. The bromination in acetic acid was accompanied by the formation of ammonium bromide, which precipitated from the solution. Refluxing of the β-bromoaminocrotononitrile with 25% hydrochloric acid decomposed the molecule into α-hydroxyacetone, which yielded a bright orange 2,4-dinitrophenylhydrazone, melting at 108.5-109°C. This showed that the bromine atom was attached to the nitrogen atom rather than to the α-carbon atom.

The bromination of β-aminocrotononitrile in aqueous solution was continued beyond the point of initial permanent yellow coloration of the solution. When approximately four moles of bromine had been added for each mole of β-aminocrotononitrile, the color of the solution had changed through yellow, orange, and was a light straw yellow. A darker colored oil was observed in the bottom of the flask. The oil was extracted with ether, dried and distilled under reduced pressure to a colorless oil, which contained 66% bromine. The oil was fairly stable when freshly distilled, but, if left standing for any length of time, it fumed in moist air and precipitated ammonium bromide. The bromine content was the same as dibromo-β-aminocrotononitrile. The oil was quite lachrymatory, suggesting an α-bromo substitution. The oil is believed to be α-bromo-β-bromoaminocrotononitrile (LIX),

$$CH_3-\underset{HNBr}{\underset{|}{C}}=\overset{Br}{\overset{|}{C}}-CN \rightleftharpoons CH_3-\underset{NBr}{\underset{\|}{C}}-\overset{Br}{\overset{|}{C}}H-CN$$

(LIX) (LIX A)

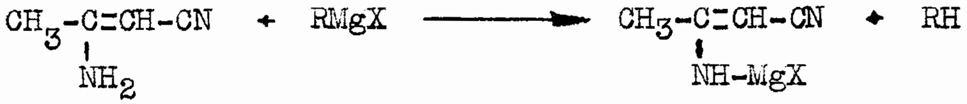
or its tautomer (LIX A)

After standing for several months, a considerable amount of material precipitated from the oil. It crystallized readily from benzene to fine white needles, melting at 156-156.5°C.

The empirical formula for this compound is $C_2H_3NBr_2$. No structure has been assigned to this compound as yet.

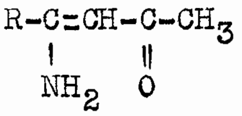
REACTION OF β-AMINOCROTONONITRILE WITH AROMATIC GRIGNARD REAGENTS

In 1951, Reynolds, Humphlett, Swamer and Hauser (51) reported the first reactions of β-aminocrotononitrile with Grignard reagents. They reacted β-aminocrotononitrile with an equivalent amount of Grignard reagent, and found that the hydrogen atom of the amino group was substituted by the MgX radical, and a molecule of hydrocarbon was liberated, according to the following reaction.



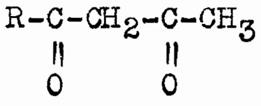
$$CH_3\text{-}\underset{NH_2}{\underset{|}{C}}{=}CH\text{-}CN + RMgX \longrightarrow CH_3\text{-}\underset{NH\text{-}MgX}{\underset{|}{C}}{=}CH\text{-}CN + RH$$

The present investigations were carried out to determine whether β-aminocrotononitrile reacted normally with an excess of aromatic Grignard reagents. It is found that, in general, the reaction proceeded with a three-fold excess of Grignard reagent



$$R\text{-}\underset{NH_2}{\underset{|}{C}}{=}CH\text{-}\underset{O}{\underset{\|}{C}}\text{-}CH_3$$

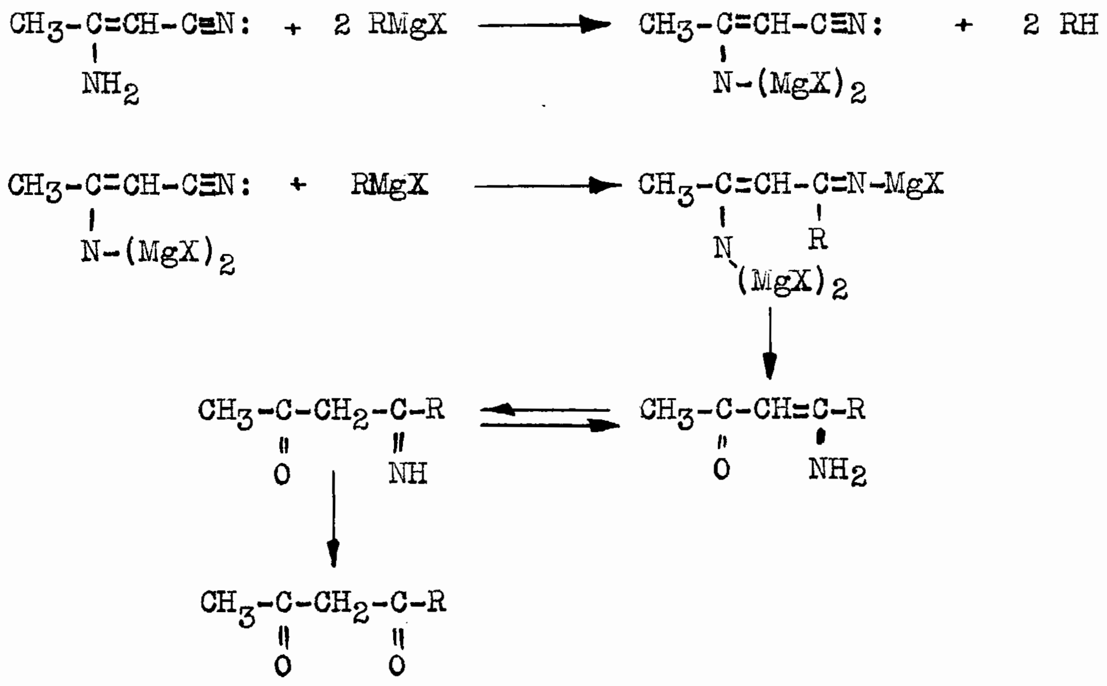
(LX)



$$R\text{-}\underset{O}{\underset{\|}{C}}\text{-}CH_2\text{-}\underset{O}{\underset{\|}{C}}\text{-}CH_3$$

(LXI)

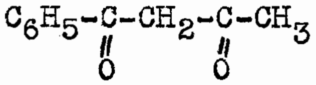
in the normal manner to produce aryl substituted β-aminoketones (LX), and β-diketones (LXI). The reaction of β-aminocrotononitrile with an equivalent quantity, or a two-fold excess of Grignard reagent produced an addition product, which yielded the original β-aminocrotononitrile when decomposed with ammonium chloride solution. The aminoketones (LX) were produced only when a three-fold or four-fold excess of Grignard reagent was employed. The first two Grignard molecules removed the active hydrogen from the β-aminocrotononitrile, as indicated in the following reactions, which are now proposed as the mechanism of reaction of β-aminocrotononitrile with aromatic Grignard reagents.



R = C_6H_5 , α-$C_{10}H_7$, o-$CH_3C_6H_4$, p-$CH_3C_6H_4$, $C_6H_5CH_2$.

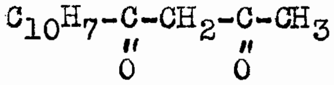
Only three of the diketones have been isolated in the present investigations. They are 1-phenyl-1,3-butadione (LXII), 1-(α-naphthyl)-1,3-butadione (LXIII), and 1-(p-tolyl)-1,3-butadione (LXIV).

1-Phenyl-1,3-butadione (LXII), or benzoyl acetone, had been known for some time. It was a white, sweet smelling crystalline material, melting at 60-61°C. It gave a bright red coloration with ferric chloride solution. Benzoyl acetone reacted readily with hydrazine and hydroxylamine to produce 3-methyl-5-phenylpyrazol, and 3-methyl-5-phenylisoxazol respectively.



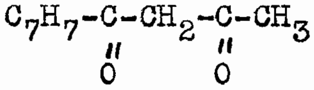
$$C_6H_5-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

(LXII)



$$C_{10}H_7-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

(LXIII)



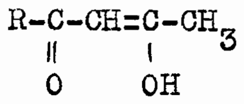
$$C_7H_7-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

(LXIV)

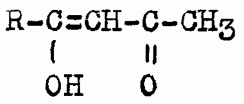
1-(α-Naphthyl)-1,3-butadione (LXIII) was first prepared in 1940 by Banchetti (4) by the addition of α-acetylnaphthalene to a cold suspension of sodium wire in dry ethyl acetate. He listed only the boiling point of the compound. It was 205-210°C at 20 mm. pressure. The present investigations have found the compound to be white crystalline needles, melting at 106-107°C. It gave a bright red coloration with ferric chloride solution, and condensed with hydroxylamine to produce 3-methyl-5-(α-naphthyl)-isoxazol, melting at 140-140.5°C.

1-(p-Tolyl)-1,3-butadione (LXIV) was prepared by Basu (5) in 1931, by the addition of p-methyl-acetophenone to a cold suspension of sodium in dry ethyl acetate, the resulting sodium salt being decomposed by 30% acetic acid. Boese (15) also prepared (LXIV) by treatment of toluene with diketene in the presence of aluminum chloride, suitably at 45-55°C. The boiling point was listed by Basu as 132°C. at 15 mm. pressure. The present investigations found the compound to be light crystals, melting at 28°C. It gave a bright red coloration with ferric chloride solution. The reaction of (LXIV) with hydroxylamine yielded 3-methyl-5-(p-tolyl)isoxazol, melting at 86-87°C.

The red coloration obtained by the action of ferric chloride solution on the diketones indicated that an enolic structure, rather than the dicarbonyl structure, represented the structure of the diketones. There are two enolic structures, (LXV) and (LXVI), which could represent the molecule. They are not equivalent structures.

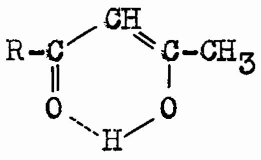

$\mathrm{R-\underset{O}{\underset{\|}{C}}-CH=\underset{OH}{\underset{|}{C}}-CH_3}$

(LXV)

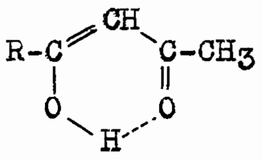

$\mathrm{R-\underset{OH}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3}$

(LXVI)

Considerable hydrogen bonding has been found previously in 1,3-diketones, with the result that structures (LXVII) and (LXVIII) could be written for the diketones.

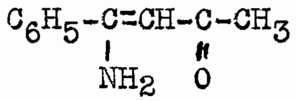


(LXVII)



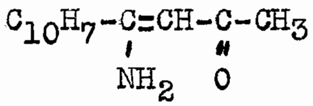
(LXVIII)

The reactions of β-aminocrotononitrile with phenyl magnesium bromide, α-naphthyl magnesium bromide, p-tolyl magnesium bromide, o-tolyl magnesium bromide, and benzyl magnesium chloride yielded the appropriate β-aminoketones in varying small yields. Only one aminoketone was isolated from each reaction. It possessed one of two possible structures, either (LXXIV) or LXXV), as well as the resonating structures of each.



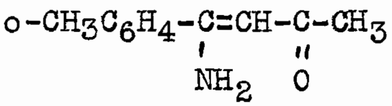
$C_6H_5-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

(LXIX)



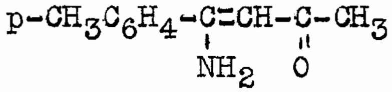
$C_{10}H_7-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

(LXX)



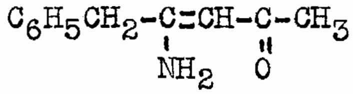
$o-CH_3C_6H_4-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

(LXXI)



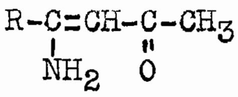
$p-CH_3C_6H_4-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

(LXXII)



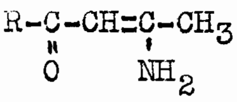
$C_6H_5CH_2-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

(LXXIII)



$R-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$

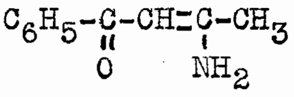
(LXXIV)



$R-\underset{O}{\underset{\|}{C}}-CH=\underset{NH_2}{\underset{|}{C}}-CH_3$

(LXXV)

Both 1-amino-1-phenylbutene-1-one-3 (LXIX) and 3-amino-1-phenylbutene-2-one-1 (LXXVI) had been prepared previously by

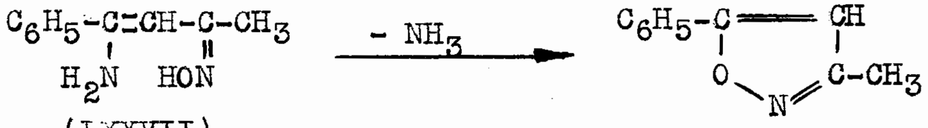


$C_6H_5-\underset{O}{\underset{\|}{C}}-CH=\underset{NH_2}{\underset{|}{C}}-CH_3$

(LXXVI)

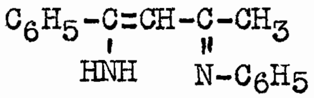
Claisen in 1926. (LXIX) was prepared by Claisen by long heating of (α-ethoxybenzylidene)acetone with methanolic ammonia in a sealed tube at 100°C. It was crystalline, and melted at 86-87°C. (LXXVI) was prepared by heating 2-ethoxy-1-benzoylpropene-1 in a sealed tube with a methanol solution of ammonia at 100°C. (LXXVI) was also prepared by treatment of 3-methyl-5-phenylisoxazol with phenyl magnesium bromide in ether, and distilling the product. It was crystalline, and melted at 143°C. The aminoketone isolated from the reaction of phenyl magnesium bromide and β-aminocrotononitrile was an oil, and gave typical ketonic derivatives. The oil reacted with hydroxylamine hydrochloride to produce 5-phenyl-3-

methylisoxazol. This latter compound was presumed to be the result of the elimination of ammonia from the oxime of 1-phenyl-1-aminobutene-1-one-3 (LXXVII), as in the equation:



(LXXVII)

The 3-methyl-5-phenylisoxazol could only be formed if the =N-OH group, and therefore the carbonyl group of the aminoketone, was adjacent to the methyl group. As further proof of the position of the carbonyl group, β-phenylaminocrotononitrile was reacted with phenyl magnesium bromide. The main product was a yellow crystalline amine, melting at 86-87°C. It was 1-phenyl-1-amino-3-phenyliminobutene-1 (LXXVIII).

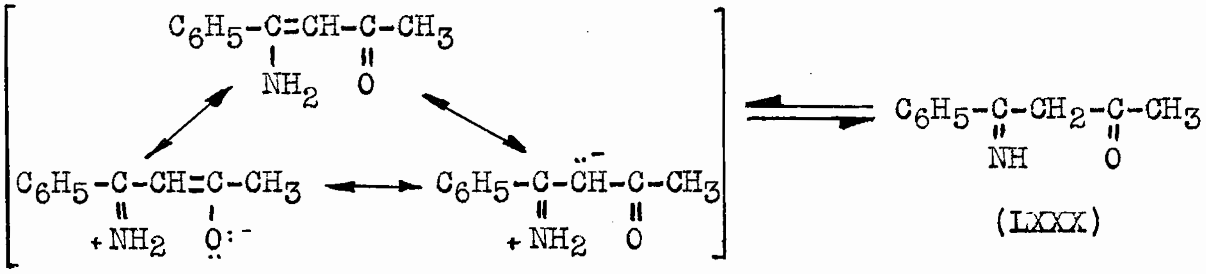


$$C_6H_5-\underset{\substack{|\\ HNH}}{C}=CH-\underset{\substack{\|\\ N-C_6H_5}}{C}-CH_3$$

(LXXVIII)

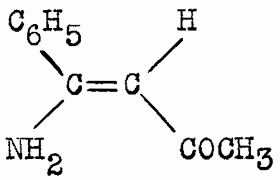
Hydrolysis of (LXXVIII) with 75% sulphuric acid produced a small amount of aminoketone, which yielded a 2,4-dinitrophenylhydrazone identical to that formed from the product of the reaction of β-aminocrotononitrile and phenyl magnesium bromide. This placed the carbonyl group adjacent to the methyl group, rather than adjacent to the aryl group, as indicated in structure (LXIX).

In general, the aminoketones isolated in this investigation were all liquids, boiling at fairly low temperatures under reduced pressure. The failure of the compounds to give a coloration with ferric chloride solution indicated that the shift of the hydrogen of the methylene group was in the direction of amine formation rather than enol formation. There would be an equilibrium set up between the β-ketiminoketone (LXXX) and the β-enaminoketone (LXXIX), as in the following equilibrium equation. 1-Phenyl-1-aminobutene-1-one-3 is used as the example.

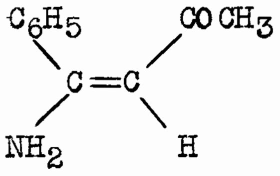


(LXXIX)

The aminoketonic structure will be the more stable of the two tautomeric forms, being stabilized by the resonating ionic structures. In addition, two of the aminoketonic structures have both of the unsaturated bonds in the side chain conjugated with each other, and with the benzene ring. The iminoketone has only one of the double bonds conjugated with the benzene ring. The fact that two compounds have been identified as 1-phenyl-1-aminobutene-1-one-3 is now believed to be due to the cis-trans isomerism of the enaminoketone. The two isomers would be represented by the structures (LXXXI) and (LXXXII).

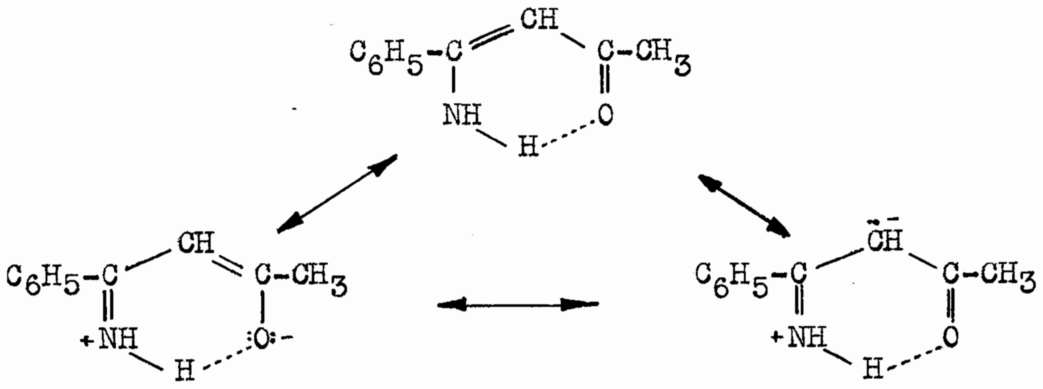


CIS (LXXXI)

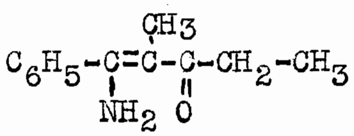


TRANS (LXXXII)

The aminoketone (LXIX), isolated during the course of the present investigations, is assumed to be the cis form, because it has the lower melting point of the two known isomers. The aminoketone, isolated by Claisen, is given the trans configuration. The cis modification can be stabilized by the formation of a hydrogen bridge, as in the case of the β-diketones. The stabilized molecule would be represented by the following structures, with lesser contributions to stability from the ionic structures.



The reaction of aromatic Grignard reagents with β-aminonitriles was extended to include the reaction of β-imino-α-methylvaleronitrile (LVI). The reaction of phenyl magnesium bromide in three-fold excess with (LVI) was accomplished in the usual manner, with the addition product being decomposed by ammonium chloride solution. The main product was identified as 1-phenyl-1-amino-2-methylpentene-1-one-3 (LXXXIII). It was a colorless



$$C_6H_5-\underset{NH_2}{C}=\overset{CH_3}{C}-\underset{\overset{\|}{O}}{C}-CH_2-CH_3$$

(LXXXIII)

oil, distilling at 80-100°C. at 8 mm. pressure. The yield was 5.2 gm., or 15% of theory. (LXXXIII) reacted with 2,4-dinitrophenylhydrazine to yield a bright orange 2,4-dinitrophenylhydrazone, melting at 230-231°C.

EXPERIMENTAL TECHNIQUES

The reaction of β-aminocrotononitrile with aryl Grignard reagents was quite straight forward. The normal precautions were taken in the preparation of the Grignard reagent. The magnesium was washed with dilute acetic acid, water, alcohol, and finally with ether. It was dried at 110°C. for several hours before use. The ether was dried over sodium metal, and freshly distilled for each reaction. The aryl halides were dried over anhydrous calcium chloride, and freshly distilled before use. The entire apparatus was flushed with dry nitrogen just before use.

The immediate product of the Grignard reagent and the β-aminocrotononitrile was a dark oil, which settled to the bottom of the flask. If the mixture was refluxed for too long, the oil became very viscous, and sometimes became amorphous. Decomposition of the complex was accomplished in three ways; with ice cold ammonium chloride solution, cold dilute hydrochloric acid, or by dry ammonia gas in toluene. The reaction of β-aminocrotononitrile with phenyl magnesium bromide was investigated more thoroughly than the reactions of the other Grignard reagents. When one or two moles of Grignard reagent were reacted with one mole of β-aminocrotononitrile, only slight traces of the diketone, benzoyl acetone, were isolated from the product. The original β-aminocrotononitrile was the main product isolated. When three or four moles of Grignard reagent were reacted with β-aminocrotononitrile, the yields of the diketone varied from 10 to 15% of theory. The yields of 1-phenyl-1-aminobutene-1-one-3 were approximately 20% of theory. The use of cobalt chloride as a catalyst in the reaction of three moles of phenyl magnesium bromide with β-aminocrotononitrile did not raise the yields of the diketone or the aminoketone. Decomposition of the Grignard complex with dilute hydrochloric acid, and by ammonia gas, produced only 1-phenyl-1-aminobutene-1-one-3 in small traces, and the 1-phenyl-1,3-butadione in 5-6% yields.

Often included in the by-products of the Grignard reactions was a small amount of white crystalline material, needles, melting at 183-184°C. It was obtained during the distillation of the aminoketone, distilling at 100-180°C at 4 mm. pressure. It had an empirical formula of $C_8H_{13}N_3O_2$, and yielded a picrate, melting at 233-233.5°C. It was soluble in alcohol, and was insoluble in ether. It was not obtained in all reactions, but was obtained at least once in the reaction of each Grignard reagent with β-aminocrotononitrile, except in the reaction with benzyl magnesium chloride. Its structure has not yet been elucidated

EXPERIMENTAL

PREPARATION OF β-AMINOCROTONONITRILE.

Preparation of Sodium Salt of β-Aminocrotononitrile.

A one-liter round bottom flask was fitted with a reflux condenser and a calcium chloride drying tube. A solution of acetonitrile (246 gm.) in 500 ml. of benzene (dried over sodium) was introduced into the flask and cooled in ice water. Metallic sodium (92 gm.) was added to the cooled solution in thin slices through the condenser at such a rate that the solution refluxed gently. Methane gas was evolved during the reaction. When all of the sodium had been added, the solution was allowed to reflux by heating in an oil bath until the sodium had all reacted. The reaction was judged to be complete when the evolution of the methane gas ceases, generally after 24-30 hours. The sodium salt appeared as a heavy white precipitate, which sometimes clung to the sodium and had to be loosened by occasional shaking of the flask. When the reaction was complete, the white precipitate was removed by filtrating and washed with dry benzene to remove any unreacted acetonitrile. The yield of the sodium salt of β-aminocrotononitrile was found to be almost quantitative. It was decomposed immediately with water to yield the β-aminocrotononitrile.

Isolation of the Low Melting Modification of β-Aminocrotononitrile.

The sodium salt prepared as above was suspended in sufficient ether to make a thick slurry. Water at about 30° was gradually added to the slurry until all of the salt had decomposed. Considerable heat was generated and most of the ether evaporated. The solution was cooled to room temperature and extracted with ether to give a dark orange solution. The β-aminocrotononitrile appeared as fine crystals when the ether was evaporated. The melting point of this modification, after several crystallizations from benzene, was 51-53°C. The yield of crude product was 115 gm. or 70% of theory.

Isolation of the High Melting Modification of β-Aminocrotononitrile.

The sodium salt, prepared as above, was suspended in 500 ml. of ether and cooled in ice. Ice cold water was added gradually to the suspension until decomposition was completed. The ether solution was separated from the aqueous solution, which was then extracted with an additional 500 ml. of ether in 100 ml. portions. The ether extracts were combined and the ether removed by distillation under reduced pressure. The residue was dissolved in warm benzene and cooled. The crystalline product was removed by filtration and recrystallized from dry benzene as needles, melting at 78-83°C. When evaporated, the mother liquor from the crystallization of the high melting modification yielded the low melting modification.

Preparation of β-(Phenylamino)crotononitrile.

The low melting modification of β-aminocrotononitrile (8.2 gm.) was dissolved in 15 ml. of glacial acetic acid in a 50 ml. round bottom flask. A solution of aniline (9.3 gm.) in 5 ml. of glacial acetic acid was added, and the mixture was allowed to stand for a few minutes. Considerable heat was evolved during the reaction. When the mixture was cooled, a mass of crystals was precipitated and removed by filtration. After washing with dilute acetic acid and water, the crude material was dried and crystallized from benzene as gleaming flakes, melting at 115-116°C. The yield of the crude product was 14.0 gm. or 90% of theory.

A similar experiment, using the high melting modification of β-aminocrotononitrile, yielded the identical product in 90% yield.

BROMINATION OF β-AMINOCROTONONITRILE

BROMINATION IN AQUEOUS SOLUTION.

β-Bromoaminocrotononitrile (LVIII).

The low melting modification of β-aminocrotononitrile (8.0 gm.) was suspended in 75 ml. of water in a 250 ml. flask. A solution of bromine in 10% potassium bromide solution was added until a flocculent white precipitate appeared and the solution had turned slightly yellow in color. The precipitate was removed by filtration and recrystallized from benzene as fine white needles, melting at 122-123°C. The yield was 2.5 gm. or 15% of theory.

Anal. Calc'd for $C_4H_5N_2Br$: Br, 49.65%

Found: Br, 49.66%.

A similar experiment, using the high melting modification of β-aminocrotononitrile, gave an identical 15% yield of β-bromoaminocrotononitrile.

α-Bromo-β-bromoaminocrotononitrile (LIX).

β-Aminocrotononitrile (20.0 gm.) was suspended in 150 ml. of water in a one-liter round bottom flask equipped with an efficient stirrer. A concentrated solution of bromine in 10% potassium bromide solution (approximately 0.17 gm. of bromine per ml. of solution) was added gradually with continuous stirring. The flocculent white precipitate of β-bromoaminocrotononitrile was observed, and then, as more of the bromine solution was added, it dissolved and the solution turned yellow. When more bromine solution was added, there was a momentary cloudiness observed with each addition, and the color of the solution changed from yellow to orange, and finally back to a light straw color. At this point, the momentary cloudiness ceased to be observed. Approximately 80 gm. of bromine were added during the course of the reaction, which was judged to be complete at this point. A heavy oil was observed at the bottom of the flask. It was extracted from the water with ether. The ether solution was washed with 10% potassium bromide solution, and finally with water. The ether extract was dried over drierite, and distilled under reduced pressure. A water white oil was obtained, distilling at 80-85°C. at 5 mm. pressure. The yield was 36.0 gm. or 62% of theory.

Anal. Calc'd. for $C_4H_4N_2Br_2$: Br, 66.6%.
Found: Br, 65.6%.

Compound $C_2H_3N\ Br_2$.

A number of samples of α-bromo-β-bromoaminocrotononitrile were combined for the purpose of distillation. Before distilling, it was noticed that there was a considerable amount of crystalline material with the oil. It was removed by filtration, and recrystallized from ethanol as fine white needles, melting at 156-156.5°C.

Anal. Calc'd. for $C_2H_3NBr_2$: C, 11.94; H, 1.49; N, 6.95; Br,79.6%.
Found: C, 11.62; H, 1.60; N, 6.64; Br, 73.6, 79.4%.

BROMINATION IN ORGANIC SOLUTION.

A. Bromination in Benzene.

The low melting modification of β-aminocrotononitrile (2.0 gm.) was dissolved in 25 ml. of dry benzene in a 100 ml. flask. A solution of bromine (10 gm. of bromine in 30 ml. of dry benzene) was added dropwise until the benzene retained a slight yellow coloration. The benzene was evaporated under reduced pressure. The residue was a dark viscous oil which partially crystallized. The crystals were removed by filtration, and recrystallized from an alcohol and water mixture (50-50) as fine white needles, melting at 122-123°C. The yield was 0.5 gm., or 12% of theory. The crystalls were identified as β-bromoaminocrotononitrile, by mixed melting point determinations with pure β-bromoaminocrotononitrile (LVIII).

A similar reaction, using the high melting modification of β-aminocrotononitrile, yielded β-bromoaminocrotononitrile in 12% yield.

B. Bromination in Glacial Acetic Acid.

β-Aminocrotononitrile (2.0 gm.) was dissolved in 10 ml. of glacial acetic acid. A solution of bromine (10 gm. of bromine in 50 ml. of glacial acetic acid) was added dropwise until the momentary yellow coloration persisted. A white, inorganic precipitate was filtered from the solution, and identified as ammonium bromide. Evaporation of the acetic acid under reduced pressure left a dark viscous oil, which partially crystallized from cool benzene as fine white needles, melting at 122-123°C, and identified as β-bromoaminocrotononitrile. The yield was 5% of theory.

REACTION OF β-BROMOAMINOCROTONONITRILE WITH HYDROCHLORIC ACID.

β-Bromoaminocrotononitrile (3.2 gm.) was placed in a 50 ml. round bottom flask, fitted with a reflux condenser. A tube was lead from the top of the condenser through a trap in a dry ice-acetone mixture, and into a flask containing 40 ml. of ice cooled water. Hydrochloric acid (25 ml. of a 25% solution) was added to the nitrile, and the mixture was refluxed gently until the evolution of gas ceased. There was nothing found in the trap cooled in dry ice, but the cold water trap was found to contain a substance, which gave a bright orange precipitate with 2,4-dinitrophenylhydrazine, melting at 280°C. There was not sufficient material for analysis.

The acidic mother liquor was evaporated under reduced pressure to yield a small amount of colorless oil, distilling over with the water. When tested with 2,4-dinitrophenylhydrazine, it yielded a bright orange precipitate, melting at 108-108.5°C. The 2,4-dinitrophenylhydrazone was found to contain no bromine. It is believed that the derivative was the 2,4-dinitrophenylhydrazone of α-hydroxyacetone.

Anal. Calc'd. for $C_9H_{10}N_4O_5$: N, 22.0%.
Found: N, 21.7%.

REACTION OF β-AMINOCROTONONITRILE WITH AROMATIC GRIGNARD REAGENTS

REACTION WITH PHENYL MAGNESIUM BROMIDE.

The procedure outlined below is that followed in the reaction of β-aminocrotononitrile with a four-fold excess of phenyl magnesium bromide.

Reagents: Bromobenzene----------- 78.4 gm.
Magnesium-------------- 12.0 gm.
Dry Ether-------------- 400 ml.
β-Aminocrotononitrile-- 10.0 gm.

A one-liter three necked round bottom flask was equipped with an efficient reflux condenser, mercury seal stirrer, and a 125 ml. dropping funnel. The magnesium was introduced into the flask, and covered with 100 ml. of ether. A crystal of iodine was added to initiate the reaction. The bromobenzene was diluted with an equal volume of ether, and approximately one-fifth of the solution was added to the magnesium. The flask was heated gently at first until the reaction of the magnesium with the bromobenzene had begun. The heat was removed, and the reaction proceeded under its own heat. Occasional external cooling was necessary to prevent too vigorous refluxing of the ether solution. When the reaction had become less vigorous, the remainder of the bromobenzene solution was added at such a rate that the mixture refluxed gently without external sources of heat. When all of the bromobenzene had been added, the reaction mixture was refluxed for an additional hour to ensure complete reaction of the reagents. The β-aminocrotononitrile was dissolved in sufficient dry ether, and was added to the phenyl magnesium bromide solution over a period of five to ten minutes. A dark oil separated from the solution. The mixture was then refluxed for four to six hours.

1-AMINO-1-PHENYL-1-BUTENE-3-ONE.(LXIX).

A. The Grignard complex was decomposed by the gradual addition of an ice-cold saturated aqueous ammonium chloride solution. The aqueous solution was extracted with ether. The ether extract was dried over Drierite, and distilled under reduced pressure to yield 1-amino-1-phenylbutene-1-one-3 (LXIX) as a light colorless oil, distilling at 70-80°C. at 1 mm. pressure. The yield was 5.0 gm., or 20% of theory. Biphenyl, and a viscous orange oil were obtained as by-products distilling above 100°C. at 1 mm. pressure. There was a considerable amount of non-volatile material in the distilling flask, which turned dark during the distillation.

Another by-product of the distillation was a small amount (0.3 gm.) of white needles, melting at 183-184°C, when the temperature of distillation went over 150°C at 1 mm. pressure. It had an empirical formula of $C_8H_{13}N_3O_2$, and yielded a yellow picrate, melting at 233-233.5°C. It was soluble in alcohol, but was insoluble in ether. Its constitution has not yet been determined.

The 2,4-Dinitrophenylhydrazone of (LXIX).

A mixture of 0.5 gm. of 2,4-dinitrophenylhydrazine, o.5 gm. of (LXIX), and 25 ml. of 95% ethanol was refluxed for five minutes. Concentrated hydrochloric acid (1 ml.) was added, and the solution was cooled. A bright orange precipitate immediately separated from the solution. It was removed by filtration, and recrystallized from benzene as fine needles, melting at 241-242°C.

Anal. Calc'd. for $C_{16}H_{15}N_5O_4$: C, 56.30; H, 4.40; N, 20.53%.

Found: C, 56.28; H, 3.86; N, 20.48%.

The Semicarbazone of (LXIX).

A mixture of 1.0 gm. of semicarbazide hydrochloride and 1.5 gm. of sodium acetate was dissolved in 10 ml. of water. This solution was added to a solution of 0.5 gm. of (LXIX) in 5 ml. of glacial acetic acid. The mixture was warmed slightly, shaken, and allowed to cool. The crystals of the semicarbazone were filtered from the solution, and recrystallized from ethanol as white needles, melting at 198-199°C.

Anal. Calc'd. for $C_{11}H_{14}N_4O$: C, 60.55; H, 6.42; N, 25.70%.

Found: C, 60.90; H, 6.00; N, 25.53%.

Action of Hydroxylamine With (LXIX).

A mixture of 0.5 gm. of hydroxylamine hydrochloride, 2.0 gm. of potassium hydroxide, and 0.5 gm. of (LXIX) was refluxed for two hours. The mixture was cooled, diluted with 50 ml. of cold water, and filtered. The filtrate was acidified with hydrochloric acid, and cooled in an ice chest. The precipitated isoxazol was recrystallized from alcohol as white needles, melting at 66-67°C.

Anal. Calc'd. for $C_{10}H_9NO$: N, 8.81%.

Found: N, 8.70%.

1-PHENYL-1,3-BUTADIONE (LXII).

A. Following decomposition of the Grignard complex, and extraction with ether, the strongly alkaline aqueous solution was neutralized with hydrochloric acid, and cooled. A precipitate of 1-phenyl-1,3-butadione (LXII) was removed by filtration, and was recrystallized from ethanol as white needles, melting at 60-61°C. The yield was 1.0 gm., or 5% of theory. It gave a bright red coloration with ferric chloride solution.

B. The ether extract of the decomposed Grignard reaction mixture was repeatedly extracted with 20 ml. portions of saturated aqueous sodium bicarbonate solution until the aqueous portion was colorless. The bicarbonate solution was acidified with hydrochloric acid, and cooled in ice. The crop of crystalline material was removed by filtration, and recrystallized from ethanol as white needles, melting at 60-61°C. The yield was 2.0 gm., or 10% of theory.

C. The Grignard reaction complex was decomposed with ice-cold dilute hydrochloric acid. The acidic solution was extracted with ether, and the ether extract was dried over Drierite. Steam distillation of the acidic aqueous residue yielded a small quantity of 1-phenyl-1,3-butadione, melting at 60-61°C. The yield was 0.5 gm., or 5% of theory.

Distillation of the dried ether extract under reduced pressure yielded 4.0 gm. of a mixture of biphenyl and an orange viscous oil, distilling at 120-170°C. at 2 mm. pressure.

D. Following the reaction of β-aminocrotononitrile with phenyl magnesium bromide, most of the ether was removed by distillation, and was replaced by an equal volume of dry toluene.

The solvent mixture was distilled until the temperature of distillation reached 100°C. The mixture was then heated under reflux for three hours at 80°C. Anhydrous ammonia gas was passed through the cooled toluene solution until all of the dark oil had disappeared. The solution was allowed to stand overnight, and was then filtered. The filtrate was evaporated under reduced pressure to yield 2.5 gm. of biphenyl, melting at 69-70°C. The solid precipitate was dissolved in ice-cold ammonium chloride solution, and extracted with ether. The ether extract was treated with a saturated aqueous solution of sodium bicarbonate, from which 1-phenyl-1,3-butadione (LXII) was obtained by acidification with hydrochloric acid. The yield was 0.3 gm., or 6% of theory.

Reaction of Hydroxylamine With (LXII).

The 1-phenyl-1,3-butadione was treated with hydroxylamine hydrochloride by a procedure similar to that described previously on page 70. The product was recrystallized from ethanol as needles, melting at 66-67°C, and identified as 3-methyl-5-phenylisoxazol.

Anal. Calc'd. for $C_{10}H_9NO$: N, 8.81%.

Found: N, 8.70%.

COBALT CHLORIDE AS A CATALYST IN THE REACTION.

A 1 mole per cent suspension of dry cobalt chloride was employed in the reaction of phenyl magnesium bromide with β-aminocrotononitrile. The yield of (LXIX) was 20% of theory, and the yield of (LXII) was 10% of theory.

REACTION WITH α-NAPHTHYL MAGNESIUM BROMIDE.

The procedure outlined below is that followed in the reaction of β-aminocrotononitrile with a three-fold excess of α-naphthyl magnesium bromide.

Reagents: α-Bromonaphthalene------ 78.0 gm.
Magnesium--------------- 9.0 gm.
Dry Ether--------------- 500 ml.
β-Aminocrotononitrile--- 10.0 gm.

The preparation of the Grignard reagent was accomplished in the same manner as the phenyl magnesium bromide. The reaction mixture was refluxed for two hours following the addition of the bromonaphthalene, in order to ensure complete reaction. The β-aminocrotononitrile was dissolved in sufficient ether, and was added to the cooled Grignard reagent over a period of ten to fifteen minutes. A dark oil separated from the solution, which was refluxed for four hours.

Decomposition was accomplished by the gradual addition of an ice-cold saturated aqueous ammonium chloride solution to the cooled reaction mixture. The alkaline aqueous solution was extracted with ether, and the ether portions were combined. The ether was evaporated under reduced pressure. The residue was steam distilled to remove the naphthalene produced by the reaction of the Grignard reagent with the active hydrogen of the amino group, and by the decomposition of excess Grignard reagent. The residue, following steam distillation, was extracted with ether. The ether extract was dried over Drierite.

1-AMINO-1-(α-NAPHTHYL)BUTENE-1-ONE-3 (LXX).

The dried ether extract of the steam distillation residue was distilled under reduced pressure, yielding a light oil, distilling at 130-135°C at 1 mm. pressure. The yield was 6.5 gm., or 25.2% of theory. The oil failed to give any coloration with ferric chloride solution.

Anal. Calc'd. for $C_{14}H_{13}NO$: N, 6.48%.

Found: N, 6.30%.

The 2,4-Dinitrophenylhydrazone of (LXX).

The oil, (LXX), was treated with 2,4-dinitrophenylhydrazine by a procedure similar to that described on page 69. The product was recrystallized from benzene as fine orange needles, melting at 216-217°C.

Anal. Calc'd. for $C_{20}H_{17}N_5O_4$: C, 61.38; H, 4.35; N, 17.90%.

Found: C, 61.44; H, 4.14; N, 17.61%.

The Semicarbazone of (LXX).

The oil, (LXX), was treated with semicarbazide hydrochloride by the procedure previously described on page 70. The product was recrystallized from ethanol as white plates, melting at 213-214°C.

Anal. Calc'd. for $C_{15}H_{16}N_4O$: C, 67.16; H, 5.97; N, 20.90%.

Found: H, 5.80; N, 20.16%.

Reaction of Hydroxylamine With (LXX).

The oil, (LXX), was treated with hydroxylamine hydrochloride by the procedure previously described on page 70. The product was recrystallized from ethanol as white plates, melting at 140-141°C.

Anal. Calc'd. for $C_{14}H_{11}NO$: N, 6.70%.

Found: N, 7.26%.

1-(α-NAPHTHYL)-1,3-BUTADIONE (LXIII).

The ether extract of the decomposed Grignard reaction mixture was repeatedly extracted with 20 ml. portions of saturated aqueous sodium bicarbonate solution until the aqueous extracts were colorless. The bicarbonate extract was neutralized with hydrochloric acid, and cooled. A crop of crystals appeared, and was filtered from the solution. The product was recrystallized from ethanol as fine prisms, melting at 107-108°C. It gave a bright red coloration with ferric chloride solution. The yield was 1.5 gm., or 5.8% of theory.

Anal. Calc'd. for $C_{14}H_{12}O_2$: C, 79.25; H, 5.66%.

Found: C, 79.27; H, 5.99%.

REACTION WITH o-TOLYL MAGNESIUM BROMIDE.

The procedure outlined below was that followed in the reaction of β-aminocrotononitrile with a three-fold excess of o-tolyl magnesium bromide.

Reagents:		
	o-Bromotoluene----------	64.2 gm.
	Magnesium---------------	9.0 gm.
	Dry Ether---------------	400 ml.
	β-Aminocrotononitrile--	10.0 gm.

The preparation of the Grignard reagent was accomplished in the same manner as the phenyl magnesium bromide. The reaction mixture was refluxed for six hours to ensure complete reaction of the magnesium. The β-aminocrotononitrile was dissolved in sufficient ether, and added to the cooled Grignard reagent over a period of ten to fifteen minutes. The reaction mixture was refluxed for six hours. Decomposition was accomplished by the gradual addition of an ice-cold saturated aqueous ammonium chloride solution to the cooled reaction mixture. The aqueous solution was extracted with ether. The ether extract was dried over anhydrous sodium sulphate.

1-(o-TOLYL)-1-AMINOBUTENE-1-ONE-3 (LXXI).

The dried ether extract was distilled under reduced pressure to yield 1-(o-tolyl)-1-aminobutene-1-one-3 as a light yellow oil, distilling at 40-50°C. at 4 mm. pressure. The yield was 2.5 gm., or 11% of theory.

The 2,4-Dinitrophenylhydrazone of (LXXI).

(LXXI) was treated with 2,4-dinitrophenylhydrazine by the procedure outlined on page 69. The product was crystallized from benzene as light orange needles, melting at 162-163°C.

Anal. Calc'd. for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.79; N, 19.72%.

Found: C, 57.81; H, 4.25; N, 19.41%.

REACTION WITH p-TOLYL MAGNESIUM BROMIDE.

The procedure outlined below was that followed in the reaction of β-aminocrotononitrile with a three-fold excess of p-tolyl magnesium bromide.

Reagents:		
	p-Bromotoluene	64.2 gm.
	Magnesium	9.0 gm.
	Dry Ether	400 ml.
	β-Aminocrotononitrile	10.0 gm.

The p-tolyl magnesium bromide was prepared in the usual manner, refluxing the solution for six hours to ensure complete reaction with the magnesium. The β-aminocrotononitrile was dissolved in sufficient ether, and was added to the cooled Grignard reagent over a period of ten to fifteen minutes. The mixture was then refluxed for an additional six hours. The decomposition of the Grignard complex was accomplished by the gradual addition of an ice-cold saturated aqueous solution of ammonium chloride.

1-(p-TOLYL-1,3-BUTADIONE (LXIV).

A. The decomposed Grignard solution was extracted with ether. The ether extract was repeatedly extracted with 20 ml. portions of saturated aqueous sodium bicarbonate solution. The bicarbonate solution was acidified with hydrochloric acid, and cooled. A small amount of crystalline material, melting at 28°C., separated from the solution. The yield was 0.2 gm., or 1% of theory. It gave a bright red coloration with ferric chloride solution.

B. Following ether extraction of the decomposed Grignard complex, the alkaline aqueous residue was acidified with hydrochloric acid, and was cooled. The yield of crystalline 1-(p-tolyl)-1,3-butadione, melting at 28°C., was 0.1 gm., or 0.5% of theory.

The Reaction of Hydroxylamine With (LXIV).

(LXIV) was treated with hydroxylamine by the procedure outlined on page 70. The product was recrystallized from ethanol to white needles, melting at 88-90°C. There was insufficient material for analysis.

1-AMINO-1-(p-TOLYL)BUTENE-1-ONE-3 (LXXII).

The decomposed Grignard solution was extracted with ether. The ether extract was dried over Drierite. The ether was removed under reduced pressure, and the aminoketone (LXXII) was obtained as a light yellow oil, distilling at 30-40°C. at 4 mm. pressure. The yield was 2.5-3.2 gm., or 11-15% of theory.

The 2,4-Dinitrophenylhydrazine Reaction With (LXXII).

The oil, (LXXII), was treated with 2,4-dinitrophenylhydrazine by the procedure given on page 69. The product was recrystallized from benzene as fine bright red needles, melting at 259-260°C.

Anal. Calc'd. for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.79; N, 19.72%.

Found: C, 57.62; H, 4.58; N, 19.65%.

The Reaction of Hydroxylamine With (LXXII).

(LXXII) was treated with hydroxylamine hydrochloride by the procedure described on page 70. The product was crystallized from ethanol as white needles, melting at 88-90°C. It was found to be identical with the product of the reaction of hydroxylamine hydrochloride and 1-(p-tolyl)-1,3-butadione.

p,p'-BITOLYL.

After the 1-amino-1-(p-tolyl)butene-1-one-3 had been distilled, a higher boiling fraction, distilling at 110-180°C at 4 mm. pressure, was obtained as a viscous yellow oil, which yielded 2.0 gm. of a white crystalline material. This material crystallized from ethanol as white plates, melting at 120-121°C. It was identified as p,p'-bitolyl.

REACTION WITH BENZYL MAGNESIUM CHLORIDE.

The procedure outlined below was that followed in the reaction of β-aminocrotononitrile with a four-fold excess of benzyl magnesium chloride.

Reagents: Benzyl Chloride-------- 62.4 gm.
Magnesium-------------- 12.0 gm.
Dry Ether-------------- 400 ml.
β-Aminocrotononitrile-- 10.0 gm.

The benzyl magnesium chloride was prepared in the usual manner, refluxing for one hour. The β-aminocrotononitrile was dissolved in sufficient ether, and was added to the Grignard reagent over a period of ten to fifteen minutes. The mixture was refluxed for an additional five hours. The Grignard complex was decomposed and worked up in the usual manner.

2-AMINO-1-PHENYLPENTENE-2-ONE-4 (LXXIII).

Decomposition of the Grignard complex was accomplished by the gradual addition of a cold saturated ammonium chloride solution to the cooled Grignard reaction mixture. The reaction products were extracted with ether, which was then dried over anhydrous sodium sulphate. The dried ether extract was distilled under reduced pressure, yielding 2-amino-1-phenylpentene-2-one-4 as a yellow oil, distilling at 70-75°C. at 1 mm. pressure. The yield was 3.5 gm., or 16% of theory.

The 2,4-Dinitrophenylhydrazone of (LXXIII).

(LXXIII) was treated with 2,4-dinitrophenylhydrazine by the procedure outlined on page 69. The product was recrystallized from benzene as orange needles, melting at 146-147°C.

Anal. Calc'd. for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.79; N, 19.72%.

Found: C, 57.53; H, 4.78; N, 19.62%.

p,p'-BIBENZYL.

Following the distillation of (LXXIII), the higher boiling fraction, distilling at 110-180°C. at 1 mm. pressure, yielded a small amount of white crystalline material, which melted at 52.5°C. It was presumably p,p'-bibenzyl. In addition, a small amount of viscous oil was obtained.

REACTION OF PHENYL MAGNESIUM BROMIDE WITH
β-PHENYLAMINOCROTONONITRILE

The procedure outlined below was that followed in the reaction of β-phenylaminocrotononitrile with a three-fold excess of phenyl magnesium bromide.

Reagents:		
	Bromobenzene	117.6 gm.
	Magnesium	18.1 gm.
	Dry Ether	500 ml.
	β-Phenylaminocrotononitrile	19.2 gm.

The phenyl magnesium bromide was prepared in the usual manner, refluxing for one hour. One-half of the Grignard reagent was added to an ether suspension of β-phenylaminocrotononitrile over a period of thirty minutes. The mixture was then refluxed for 48 hours.

1-PHENYL-1-AMINO-3-PHENYLIMINOBUTENE-1 (LXXVIII).

Decomposition was accomplished by the gradual addition of a cold saturated ammonium chloride solution to the cooled Grignard reaction mixture. The solution was extracted with ether, which was then dried over anhydrous sodium sulphate. The ether was removed, and the residue was distilled under reduced pressure. The first fraction, boiling at 50-80°C. at 3 mm. pressure, was a light oil. It was identified as aniline. The yield was 3.5 gm. Distillation was stopped at this point, and the residue in the distilling flask was dissolved in hot ethanol, and allowed to crystallize into yellow crystals, melting at 85-86°C. The yield was 6.5 gm., or 12% of theory.

Anal. Calc'd. for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86%.

Found: C, 81.59; H, 6.70; N, 11.75%.

ACID HYDROLYSIS OF (LXXVIII) with 75% sulphuric acid at 150-160°C. for one hour yielded a small amount of oil, which gave an orange 2,4-dinitrophenylhydrazone, melting at 247-248°C. The mixed melting point with the 2,4-dinitrophenylhydrazone of (LXIX) was 243-244°C., proving them to be identical.

Anal. Calc'd. for $C_{16}H_{15}N_5O_4$: C, 56.30; H, 4.40; N, 20.53%.

Found: C, 56.22; H, 4.16; N, 20.26%.

DICHROMATE OXIDATION OF (LXXVIII) yielded a small amount of white crystalline material, melting at 120-122°C. It was identified as benzoic acid.

PREPARATION OF β-IMINO-α-METHYLVALERONITRILE (LVI)

Reagents:	Propionitrile--	76.4 gm.
	Sodium---------	21.4 gm.
	Benzene--------	200 ml.

The propionitrile was mixed with the dry benzene in a 500 ml. round bottom flask equipped with an efficient reflux condenser, and a calcium chloride drying tube. The sodium was cut into thin slices, and was added to the propionitrile through the condenser at such a rate that the mixture refluxed gently. A large amount of gas was liberated by the reaction. The gas was passed through a bromine water trap in order to remove any unsaturated gases. However, there was no change on passing the gas through the trap. After the addition of the sodium was completed, the mixture was refluxed for 22 hours, or until no more gas was evolved. The crystalline sodium salt was removed by filtration, and washed with dry benzene to remove any unreacted propionitrile.

The decomposition of the white sodium salt of β-imino-α-methylvaleronitrile was accomplished by the addition of water to a cold suspension of the sodium salt in ether. The ether extract of the aqueous solution was dried over calcium chloride, and distilled under reduced pressure. β-Imino-α-methylvaleronitrile was obtained as a viscous oil, distilling at 120-130°C. at 4 mm. pressure. The oil partially crystallized as large prisms when it was seeded with pure crystals of β-imino-α-methylvaleronitrile. The yield was 36 gm., or 71% of theory. The melting point of the product, when recrystallized from benzene, was 44-46°C.

REACTION OF PHENYL MAGNESIUM BROMIDE WITH α-METHYL-β-IMINOVALERONITRILE

The procedure outlined below was that followed in the reaction of α-methyl-β-iminovaleronitrile with a three-fold excess of phenyl magnesium bromide.

Reagents:	Bromobenzene-------------------	88.5 gm.
	Magnesium----------------------	13.7 gm.
	Dry Ether----------------------	500 ml.
	α-Methyl-β-iminovaleronitrile--	20.7 gm.

The preparation of the phenyl magnesium bromide was accomplished in the usual manner. The α-methyl-β-iminovaleronitrile was dissolved in sufficient ether, and was added to the cooled Grignard reagent over a period of ten to fifteen minutes. A dark oil separated from the solution, which was refluxed for fourteen hours.

1-PHENYL-1-AMINO-2-METHYLPENTENE-1-ONE-3 (LXXXIII).

Decomposition of the dark oil was accomplished by the gradual addition of an ice-cold saturated aqueous ammonium chloride solution to the cooled Grignard reaction mixture. The aqueous solution was extracted with ether. The ether solution was dried over Drierite, and distilled under reduced pressure to yield a light oil, distilling at 80-100°C. at 8 mm. pressure. This oil was identified as 1-phenyl-1-amino-2-methylpentene-1-one-3. The yield was 5.2 gm., or 15% of theory.

The 2,4-Dinitrophenylhydrazone of (LXXXIII).

(LXXXIII) was treated with 2,4-dinitrophenylhydrazine as described on page 69. The bright orange product was recrystallized from benzene as fine needles, melting at 230-231°C.

Anal. Calc'd. for $C_{18}H_{19}N_5O_4$: N, 18.97%.

Found: N, 18.39%.

ULTRAVIOLET ABSORPTION SPECTRA OF β-AMINOCROTONONITRILE

Solutions of both modifications of β-aminocrotononitrile were prepared in absolute ethanol, in dry acetonitrile, and in dry cyclohexane. The absorption spectra of the solutions were determined between 220 and 295 millimicrons, using a Beckmann DU Quartz Spectrophotometer.

Acetonitrile Solutions.

The acetonitrile was dried over anhydrous calcium chloride, and distilled. The concentrations of the solutions of β-aminocrotononitrile were 0.0001 moles/liter of solution, or 0.01048 gm./1000 gm. of solvent. The molar extinction coefficient was determined by multiplying the observed optical density by the term $\left(\frac{1}{C\frac{b}{m}}\right)$, which in this case had a value of 7950.

The units of the above term are as follows.

C - Concentration in gm./1000 gm. of solvent.
b - Width of absorption cell in cm.
m - Molecular weight of solute.

Absolute Ethanol Solutions.

The ethanol was dried in the normal manner by refluxing with calcium oxide, and redistilling from sodium. The concentrations of the solutions of β-aminocrotononitrile were 0.0001 moles/liter of solution, or 0.01036 gm./1000 gm. of solvent. The molar extinction coefficients were determined by multiplying the optical density by the above term, which in this case had a value of 7850.

Cyclohexane Solutions.

The cyclohexane was dried over anhydrous calcium chloride, and distilled. Saturated solutions of β-aminocrotononitrile were prepared. The solubility was very low in cyclohexane. The solutions were then diluted to one one-hundredth of that concentration. The concentrations of the final solutions were not known accurately, but were less than 0.0001 molar.

The cell widths were:

#12136 S b = 0.998 cm. for pure solvent.
#12137 S b = 0.999 cm. for solutions of high melting form.
5286 S b = 0.999 cm. for solutions of low melting form.

CALCULATION OF HEATS OF SOLUTION AND HEATS OF FUSION OF β-AMINOCROTONONITRILE MODIFICATIONS

Data For Solubility Curves of Benzene Solutions of β-Aminocrotononitrile.

Low Melting Modification.

Solubility at 289.5°A. = 8.57 gm./100 gm. of benzene.
Mole Fraction of Solute = 0.0755.
Log. Mole Fraction = -1.122.
Inverse of Absolute Temperature = 0.00346.

Melting Point.. 325°A.
Inverse of Absolute Temperature = 0.00308.
Log. Mole Fraction = 0.0.

High Melting Modification.

Solubility at 289.5°A. = 1.22 gm./100 gm. of benzene.
Mole Fraction of Solute = 0.0115.
Log. Mole Fraction = -1.939.
Inverse of Absolute Temperature = 0.00346.

Melting Point.. 352-357°A.
Inverse of Absolute Temperature = 0.00280.
Log. Mole Fraction = 0.0.

Intercept for High Melting Modification = 9.10.
Heat of Solution = 9.10 x 4.576 x 325 = 13,500 cal./mole.

Intercept for Low Melting Modification = 8.22.
Heat of Solution = 8.22 x 4.576 x 357 = 13,600 cal./mole.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF β-AMINOCROTONONITRILE IN DRY ACETONITRILE

TABLE III

	Low Melting Modification		High Melting Modification	
Wavelength	Optical Density	Molar Extinction Coefficient	Optical Density	Molar Extinction Coefficient
mμ				
224	.323	2535	.339	2660
226	.369	2900	.394	3090
228	.430	3375	.460	3630
230	.500	3925	.546	4290
232	.581	4560	.637	5000
234	.671	5260	.741	5810
236	.774	6075	.855	6720
238	.884	6940	.978	7670
240	1.000	7850	1.103	8660
242	1.111	8720	1.225	9610
244	1.214	9540	1.343	10540
246	1.318	10330	1.462	11480
248	1.413	11100	1.569	12300
250	1.497	11770	1.669	13100
252.0	1.532	12020	1.690	13280
252.5	1.544	12120	1.705	13400
253.0	1.559	12230	1.727	13580
253.5	1.570	12320	1.730	13600
254.0	1.575	12370	1.733	13620
254.5	1.583	12430	1.739	13650
255.0	1.570	12320	1.728	13580
255.5	1.570	12320	1.718	13490
256.0	1.555	12200	1.702	13360
256.5	1.555	12200	1.700	13350
257.0	1.544	12120	1.685	13230
258	1.534	12020	1.673	13120
260	1.467	11520	1.593	12500
262	1.370	10760	1.488	11680
264	1.250	9810	1.359	10680
266	1.112	8720	1.194	9370
268	.960	7540	1.026	8040
270	.794	6230	.850	6670
272	.648	5090	.690	5420
274	.508	3990	.542	4260
276	.379	2975	.402	3150
278	.271	2130	.288	2260
280	.186	1460	.197	1550
282	.122	957	.127	995
284	.076	595	.077	605
286	.048	380	.046	360
288	.031	240	.026	200
290	.021	160	.018	140

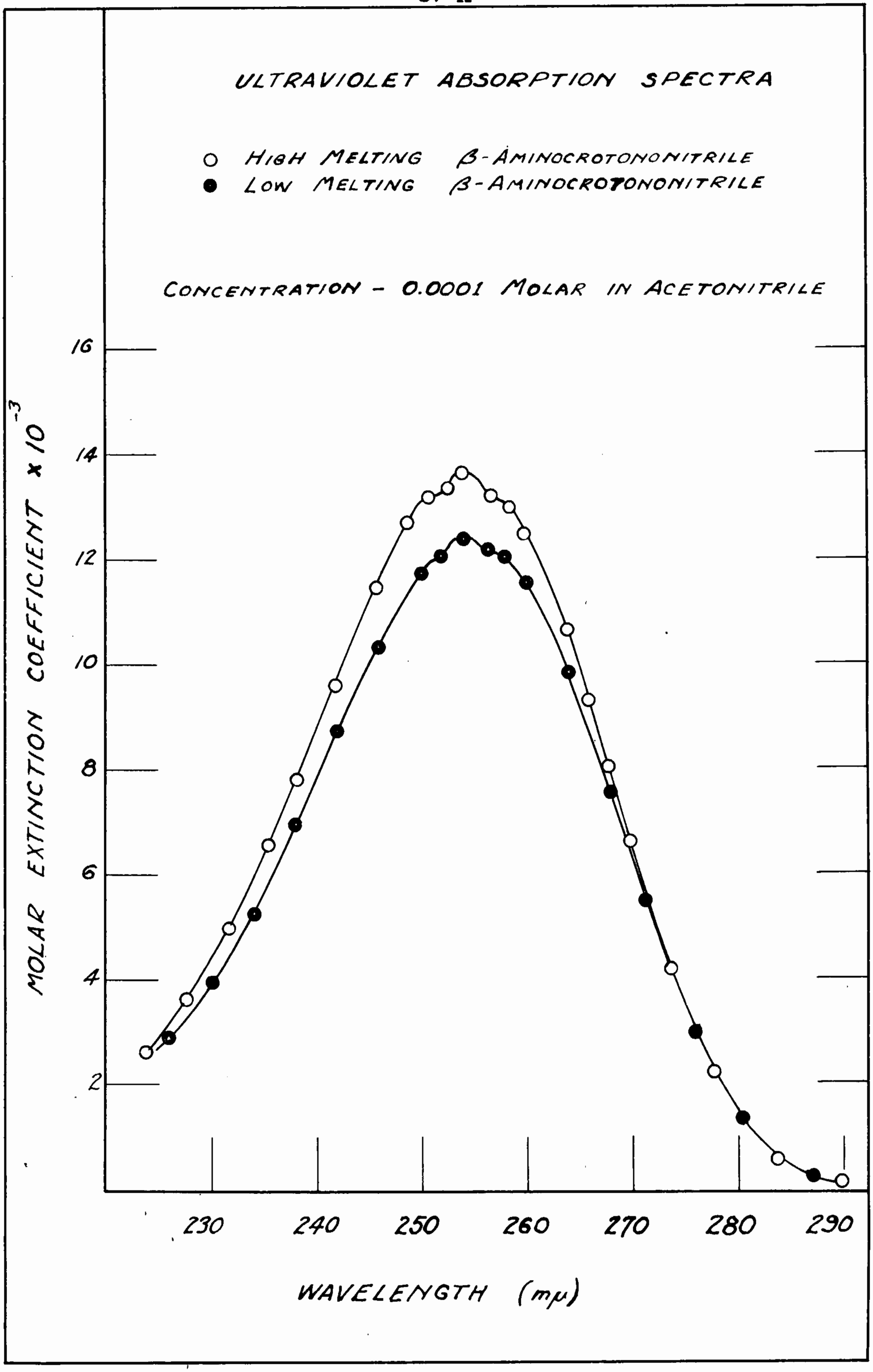

ULTRAVIOLET ABSORPTION SPECTRA
○ HIGH MELTING β-AMINOCROTONONITRILE
● LOW MELTING β-AMINOCROTONONITRILE
CONCENTRATION - 0.0001 MOLAR IN ACETONITRILE
MOLAR EXTINCTION COEFFICIENT × 10^-3
16
14
12
10
8
6
4
2
230
240
250
260
270
280
290
WAVELENGTH (mμ)

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRUM OF β-AMINOCROTONONITRILE IN ABSOLUTE ETHANOL

TABLE IV

	Low Melting Modification		High Melting Modification	
Wavelength	Optical Density	Molar Extinction Coefficient	Optical Density	Molar Extinction Coefficient
mμ				
220	.201	1600	.192	1527
221	.212	1690	.205	1630
222	.226	1800	.219	1740
223	.241	1920	.235	1870
224	.257	2045	.254	2020
225	.276	2195	.275	2185
226	.298	2370	.298	2370
227	.322	2560	.325	2580
228	.348	2770	.352	2800
229	.379	3015	.386	3070
230	.410	3260	.421	3350
231	.447	3555	.460	3660
232	.482	3840	.498	3960
233	.526	4180	.545	4340
234	.569	4530	.590	4690
235	.613	4875	.640	5090
236	.652	5180	.694	5510
237	.712	5660	.750	5960
238	.770	6120	.808	6415
239	.825	6560	.870	6910
240	.883	7020	.939	7460
241	.943	7500	1.000	7950
242	1.008	8000	1.065	8450
243	1.065	8460	1.131	9000
244	1.134	9030	1.205	9580
245	1.196	9500	1.283	10200
246	1.255	9980	1.345	10690
247	1.318	10480	1.415	11250
248	1.366	10870	1.469	11690
249	1.428	11350	1.533	12200
250	1.474	11720	1.597	12700
251	1.523	12100	1.652	13130
252	1.573	12520	1.694	13480
253	1.615	12840	1.745	13880
254	1.645	13090	1.773	14100
255	1.672	13300	1.805	14340
256	1.690	13450	1.830	14560
257	1.698	13500	1.840	14630
258	1.707	13560	1.850	14700
259	1.710	13610	1.848	14690

TABLE IV - Continued

	Low Melting Modification		High Melting Modification	
Wavelength	Optical Density	Molar Extinction Coefficient	Optical Density	Molar Extinction Coefficient
mμ				
260	1.684	13400	1.838	14610
261	1.675	13320	1.803	14330
262	1.648	13100	1.780	14150
263	1.610	12800	1.732	13790
264	1.568	12480	1.688	13410
265	1.512	12020	1.630	12960
266	1.454	11570	1.566	12440
267	1.387	11030	1.498	11900
268	1.316	10470	1.419	11290
269	1.244	9900	1.338	10630
270	1.167	9270	1.252	9950
271	1.083	8620	1.165	9240
272	1.000	7950	1.074	8540
273	.920	7310	.981	7800
274	.840	6680	.900	7160
275	.758	6030	.808	6520
276	.691	5500	.740	5890
277	.561	4460	.599	4760
278	.522	4150	.560	4450
279	.453	3600	.485	3860
280	.388	3085	.417	3315
281	.330	2625	.352	2800
282	.276	2195	.295	2345
283	.227	1805	.241	1918
284	.180	1430	.192	1528
285	.149	1185	.163	1297
286	.121	965	.125	993
287	.096	763	.099	787
288	.075	596	.077	612
289	.060	470	.059	468
290	.047	375	.045	358
291	.036	285	.034	270
292	.029	230	.025	200
293	.024	190	.020	159
294	.020	159	.015	119
295	.017	135	.012	95

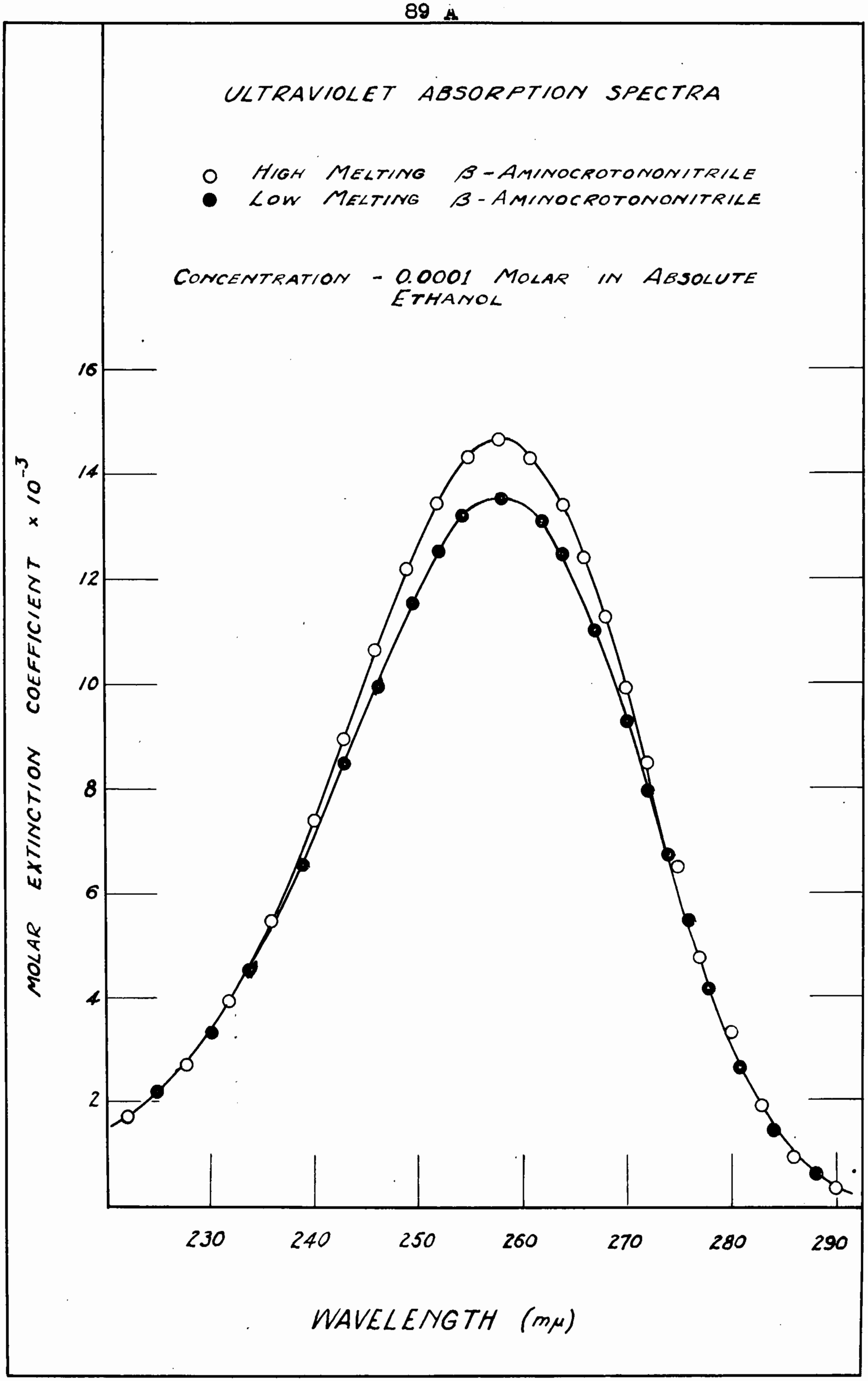

ULTRAVIOLET ABSORPTION SPECTRA
○ HIGH MELTING β-AMINOCROTONONITRILE
● LOW MELTING β-AMINOCROTONONITRILE
CONCENTRATION - 0.0001 MOLAR IN ABSOLUTE ETHANOL
MOLAR EXTINCTION COEFFICIENT × 10⁻³
16
14
12
10
8
6
4
2
230
240
250
260
270
280
290
WAVELENGTH (mμ)

TABLE V

ULTRAVIOLET ABSORPTION SPECTRUM OF β-AMINOCROTONONITRILE IN DRY CYCLOHEXANE

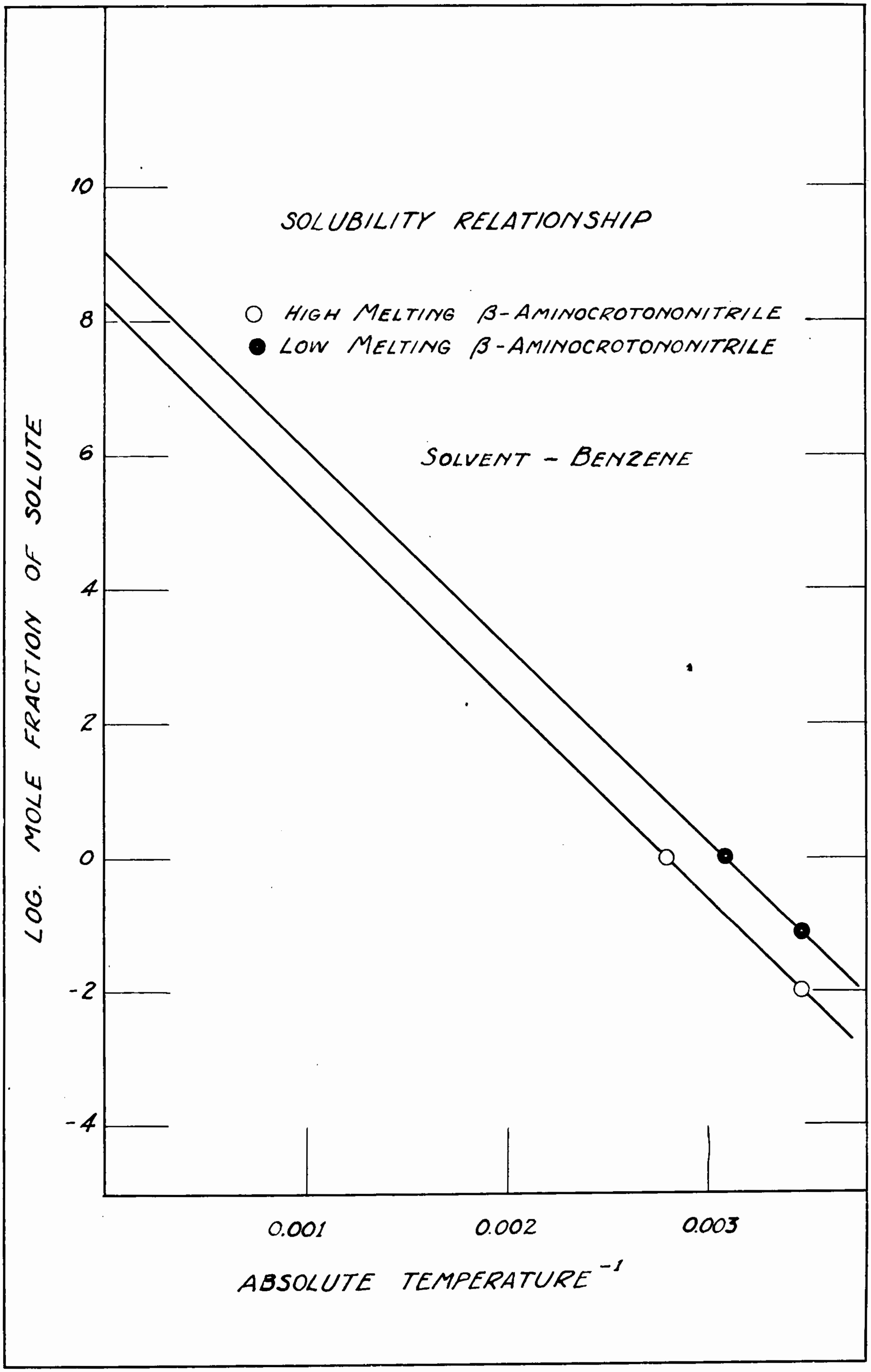
TABLE V

Wavelength	Low Melting Modification Optical Density	High Melting Modification Optical Density
mμ		
219	104.1 *	.048
220	104.1 *	.048
222	103. *	.048
224	101. *	.048
226	.007	.053
228	.023	.057
230	.043	.063
232	.063	.069
234	.080	.076
236	.105	.083
238	.126	.090
240	.148	.095
242	.167	.098
244	.182	.099
246	.190	.097
248	.196	.095
250	.198	.092
251	.196	.089
252	.193	.086
254	.184	.079
256	.172	.074
258	.154	.065
260	.136	.058
262	.115	.051
264	.093	.043
266	.071	.035
268	.052	.030
270	.036	.026
272	.022	.021
274	.010	.017
276	.004	.014
278	.000	.013
280	101. *	.013
290	101. *	.012

* Units are per cent transmission.

SOLUBILITY CURVES OF β-AMINOCROTONONITRILE

IN BENZENE


SOLUBILITY RELATIONSHIP
○ HIGH MELTING β-AMINOCROTONONITRILE
● LOW MELTING β-AMINOCROTONONITRILE
SOLVENT – BENZENE
LOG. MOLE FRACTION OF SOLUTE
10
8
6
4
2
0
-2
-4
0.001
0.002
0.003
ABSOLUTE TEMPERATURE⁻¹

SUMMARY

The structures of the two modifications of β-aminocrotononitrile have been investigated. The two modifications exhibit identical behavior toward bromine in aqueous and organic media. Aniline in glacial acetic acid reacts with both forms of β-aminocrotononitrile to produce β-phenylaminocrotononitrile in 90% yields. The ultraviolet spectra of the two modifications were taken in polar and non-polar solvents. In polar solvents, ethanol and acetonitrile, the spectra were smooth symmetrical curves with the maxima at almost identical wavelengths for both modifications in each solvent. The molar extinction coefficients of the two modifications were approximately equal in each solvent. In the non-polar solvent, cyclohexane, the curve for the low melting modification had the characteristic shape found in the polar solvents. However, the curve obtained for the high melting modification was much flatter, with a broad masking band from 220 millimicrons extending toward the shorter wavelengths. The positions of the maxima for the two modifications differed by 60 millimicrons. The data for the maxima is given in Table II on page 40. These maxima could best be explained by assuming an enamine structure for both modifications, rather than a ketimine structure. This eliminated the possibility of the two forms being enamine and ketimine tautomers. Acrylonitrile exhibits a maximum at 250 millimicrons, approximately the same position as the positions of the maxima observed for the β-aminocrotononitrile modifications. Substituted acrylonitriles are expected to have the maximum shifted toward the higher wavelengths if the groups

which are substituted into the acrylonitrile contain unshared electron pairs, or unsaturated bonds which are conjugated with the cyano group. The unshared electron pair of the amino group of β-aminocrotononitrile served to shift the maximum in the observed direction. The very high values that were obtained for the molar extinction coefficients could be explained by the resonance of the β-aminocrotononitrile molecule. All of the evidence pointed to the existence of the enamine type of bond arrangement.

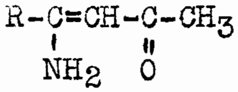
Next, the action of solvents on β-aminocrotononitrile was studied. Both modifications could be recrystallized from non-polar solvents. Crystallization of both modifications from polar solvents yielded the low melting modification exclusively. It is now proposed that the two modifications are cis and trans isomers of β-aminocrotononitrile. The low melting modification is given the cis configuration, by virtue of its higher solubility. The high melting modification is given the trans configuration, by virtue of its lower solubility. The stability of the cis isomer is due to hydrogen bonding between the amino group and the cyano group. In polar solvents, it is assumed that the contributions of the ionic resonating structures to the resonance hybrid are greater than in non-polar solvents. The ionic structures do not possess the unsaturated bond between the α- and β- carbon atoms, and the cis-trans isomerism has been destroyed. It is therefore to be expected that crystallization of either modification from a non-polar solvent would result in no change whatever, and that crystallization from a polar solvent would result in the formation of the more stable cis isomer. This is the observed case.

Enantiotropic polymorphism has been eliminated by the fact that there was no transition temperature, where the stability of the two modifications would be reversible. Each modification has a definite melting point, whereas enantiotropic polymorphic modifications have only one real melting point. Monotropic polymorphism is eliminated by the reverse stability of the two modifications. It is the high melting monotropic modification which is the stable one. The heats of fusion of polymorphic modifications would be quite different. The heats of fusion of the two modifications of β-aminocrotononitrile, as determined from their heats of solution in benzene, are found to be almost identical.

A new mechanism for the formation of β-aminocrotononitrile has been proposed, based on the modern electronic concepts. This mechanism has been applied to the formation of α-methyl-β-iminovaleronitrile.

The bromination of β-aminocrotononitrile in various solvents has been studied. Bromination in benzene and glacial acetic acid yielded β-bromoaminocrotononitrile in 10 and 5% yields. Bromination with a solution of bromine in potassium bromide solution yielded β-bromoaminocrotononitrile in 15% yield, and also yielded α-bromo-β-bromoaminocrotononitrile in 62% yield. β-Bromoaminocrotononitrile was decomposed by 25% hydrochloric acid into α-hydroxyacetone. A third bromo compound was isolated from the bromination reaction in aqueous medium. It has the empirical formula, $C_2H_3NBr_2$, but the structure has not as yet been elucidated.

The action of aromatic Grignard reagents has been investigated quite thoroughly. When one mole of β-aminocrotononitrile is reacted with one or two moles of Grignard reagent, the complex that is formed is decomposed to the original β-aminocrotononitrile by ammonium chloride solution. When three or four moles of Grignard reagent are reacted with a mole of β-aminocrotononitrile, then the reaction proceeds normally with the cyano group. The main products were β-aminoketones of the type



$$R-\underset{NH_2}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-CH_3$$

, where R is phenyl, α-naphthyl, o-tolyl, p-tolyl, and benzyl. The yields of the β-diketones, where R is phenyl, α-naphthyl, and p-tolyl are very low. The yields of the β-aminoketones range from 10 to 20% of theory. The β-aminoketones are light oils, and distillation of them must be carried out under reduced pressure. They are all characterized by typical ketonic derivatives.

Claisen had prepared 1-phenyl-1-aminobutene-1-one-3 (LXIX) in 1926, and had found it to be crystalline, melting at 86-87°C. The material isolated in the present investigations was a light oil, which showed no signs of crystallization. The two compounds are very likely cis and trans isomers. The oil is assumed to be the cis isomer, by virtue of its lower melting point, and its higher solubility. The crystalline isomer is therefore given the trans configuration. By analogy, it is presumed that the other β-aminoketones all possess the cis configuration.

The reaction of β-phenylaminocrotononitrile with phenyl magnesium bromide in excess has yielded 1-phenyl-1-aminobutene-1-phenylimine-3 in 12% yield.

The Grignard reaction with β-aminonitriles was extended to α-methyl-β-iminovaleronitrile. Phenyl magnesium bromide reacted with α-methyl-β-iminovaleronitrile to produce 1-phenyl-1-amino-2-methylpentene-1-one-3 as a light oil. The yield was 15% of theory.

CONTRIBUTIONS TO KNOWLEDGE

1. The structures of the two modifications of β-aminocrotononitrile have been elucidated. The low melting modification is the cis isomer, and the high melting modification is the trans isomer. The stability of the cis isomer is due to hydrogen bonding between the amino group and the cyano group.

2. A new mechanism has been proposed for the formation of β-aminocrotononitrile, based on the modern concepts of organic chemistry. This mechanism has been extended to cover the formation of α-methyl-β-iminovaleronitrile.

3. The ultraviolet spectra of both modifications in acetonitrile, absolute ethanol, and in cyclohexane has been investigated between 220 and 295 millimicrons.

4. β-Bromoaminocrotononitrile has been prepared in low yield by the direct bromination of β-aminocrotononitrile in benzene and in glacial acetic acid. β-Bromoaminocrotononitrile has also been prepared by bromination of an aqueous solution of β-aminocrotononitrile with a solution of bromine in potassium bromide solution. The yield was 15% of theory. Pressed bromination with the solution of bromine in potassium bromide solution yielded α-bromo-β-bromoaminocrotononitrile in 62% yield. Another bromo compound of unknown structure was isolated from the bromination product. It has the empirical formula, $C_2H_3NBr_2$. β-Bromoaminocrotononitrile is decomposed by 25% hydrochloric acid into α-hydroxyacetone.

5. The reaction of β-aminocrotononitrile with aromatic Grignard reagents in excess has been investigated. A mechanism for the reaction has been proposed. 1-Amino-1-phenylbutene-1-one-3, 1-Amino-1-(α-naphthyl)butene-1-one-3, 1-amino-1-(o-tolyl)butene-1-one-3, 1-amino-1-(p-tolyl)butene-1-one-3, and 2-amino-1-phenylpentene-2-one-4 have been prepared in yields of 10-20% by the action of phenyl magnesium bromide, α-naphthyl magnesium bromide, o- and p- tolyl magnesium bromides, and benzyl magnesium chloride. These aminoketones have been given cis configurations about the double bond in the carbon chain.

6. A by-product of the Grignard reactions, except that of the benzyl magnesium chloride, has been a small amount of white plates, melting at 183-184°C. It has a formula $C_8H_{13}N_3O_2$, and its structure has not been elucidated as yet. It forms a bright yellow picrate, melting at 233-233.5°C.

7. 1-Phenyl-1-amino-3-phenyliminobutene-1 was prepared in 12% yield by the reaction of phenyl magnesium bromide in a three-fold excess with β-phenylaminocrotononitrile. It was a bright yellow crystalline material, melting at 86-87°C.

8. 1-Phenyl-1-amino-2-methylpentene-1-one-3 has been prepared in 15% yield by the reaction of phenyl magnesium bromide in three-fold excess with α-methyl-β-iminovaleronitrile. This aminoketone is presumed to have a cis configuration about the double bond of the carbon chain.

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